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Pediatric Endocrinopathies Related to Reduced Fetal Growth

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INTRODUCTION

Over the past years, pediatric endocrinology has witnessed the fragile scaffolding of a novel concept based upon 4 solid cornerstones. The concept associates reduced prenatal growth to a series of postnatal endocrinopathies. It is currently unknown whether the latter are sequelae of the former or whether both are the result of a more fundamental defect that remains to be defined.

The *first cornerstone* for this concept—as for all medical paradigms—consists of a series of carefully documented clinical observations. The *second cornerstone* is the principle of the "critical window," originally derived from undernutrition studies in early life (Figure 1, page 2)[1,2] and nowadays established not only within the cascades of genetic switches directing tissue differentiation but also within other developmental events that proceed rapidly and are therefore vulnerable. The *third cornerstone* is the recognition that some components of the endocrine system (such as the anterior pituitary, the gonads, and the inner zone of the adrenal cortex) are more active in early life than in childhood or adulthood, implying that modulation of pronounced prenatal activity might account for some of the postnatal variations that had remained unexplained. The *fourth cornerstone* was provided by Barker and coworkers,[3] who compiled evidence consolidating the aforementioned principles as indeed applicable to endocrine-related disorders in adulthood and senescence.

Convincing evidence linking reduced prenatal growth to pediatric endocrinopathies is accumulating. This article summarizes available data on these relationships in regards to the emerging implications for clinical practice. In particular, we focus on some aspects of the somatotropic axis, adrenarche and pubarche, sexual differentiation and gonadal function, lipid metabolism, and insulin sensitivity. Most of the discussed observations concern children with either no dysmorphologic condition or with a Silver-Russell morphotype.

SOMATOTROPIC AXIS

By definition, approximately 3% of human infants are born small for gestational age (SGA), or less than the 3rd percentile. The vast majority of these infants experience an early and rapid catch-up growth and reach normal stature by 2 years of age.[4] Approximately 10% maintain a height below –2 SD, at least throughout childhood.[5,6] The mechanisms underlying the growth failure in this small percentage remain incompletely understood. In short SGA children there is an increased incidence of growth hormone deficiency (GHD), either in the classic form, which is detectable by conventional stimulation

In This Issue

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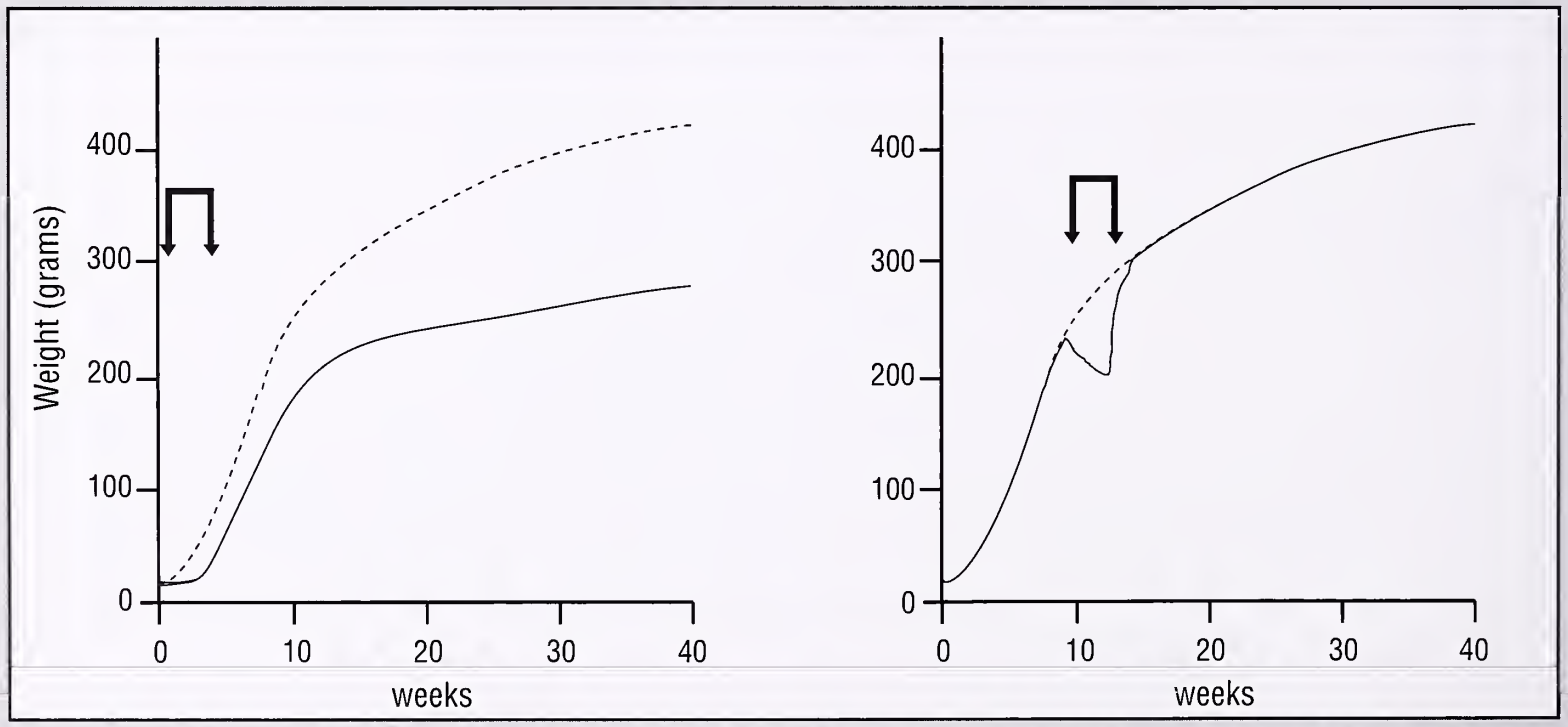
tests, or in the more subtle neurosecretory form, which is detectable by growth hormone (GH) profile studies.[7] However, the majority of short SGA children appear to be neither GHD nor GH-resistant, as indicated by basal serum levels of insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) that are within the normal range, and/or by normal IGF-1 and IGFBP-3 responses to exogenous GH, and/or by relatively low serum leptin concentrations.[8,9] Thus, available evidence points towards some form of IGF-1 resistance as the predominant factor responsible for the persistent growth failure in this group. The pathophysiology of this type of IGF-1 resistance remains to be clarified. It may have been induced by an adverse prenatal environment that programed the growth plates at a lower level of responsiveness within a critical window of time.[10-12] In addition, GHD in SGA children is commonly associated with IGF-1 resistance, which is thought to account for an average reduction of 20% in the growth-promoting efficacy of GH therapy when given to these children.[12] When a supraphysiologic dose of GH is administered (Figure 2), the growth response of short SGA children regardless of their secretory GH status readily matches that of other GHD children, indicating that the IGF-1 resistance towards growth can be overcome and that a normal height and weight can be obtained at least throughout childhood.[12] Therefore, it is anticipated that the indications and the doses for GH therapy in children will become increasingly interlinked with the emerging principles of endocrine programing in early life. GHD children, if not born SGA, are candidates for continuous GH therapy using a physiologic dose and, if born SGA, using a higher dose.

For non-GHD SGA children, the 2 major determinants of the growth response to exogenous GH are (1) the dose of GH administered and (2) the age of the child. The higher the GH dose and the younger the child, the more pronounced the response.[7,12] Two treatment avenues are being explored (Figure 3). The more conventional strategy is to treat these SGA children as if they were GHD, ie, with a continuous GH regimen using a slightly supraphysiologic dose (0.03 mg/kg/d) throughout childhood. A more innovative strategy aims at restoring the altered responsiveness within the growth plate by administering a high dose (0.07 to 0.1 mg/kg/d) of GH treatment early in life and over only 2 to 3 years. This approach results in an early and rapid normalization of body size, thus mimicking, albeit at a later age, the spontaneous catch-up growth that failed to occur in these children. More importantly, there are now preliminary data up to 5 years after GH withdrawal indicating that early and high-dose GH treatment may have the capacity to reprogram the growth pattern at a higher level in these children (Figure 4, page 4).[13] If these findings are confirmed, they may result in the development of an early and brief treatment regimen with fewer injections and an improved cost:benefit ratio compared with the more conventional strategy.

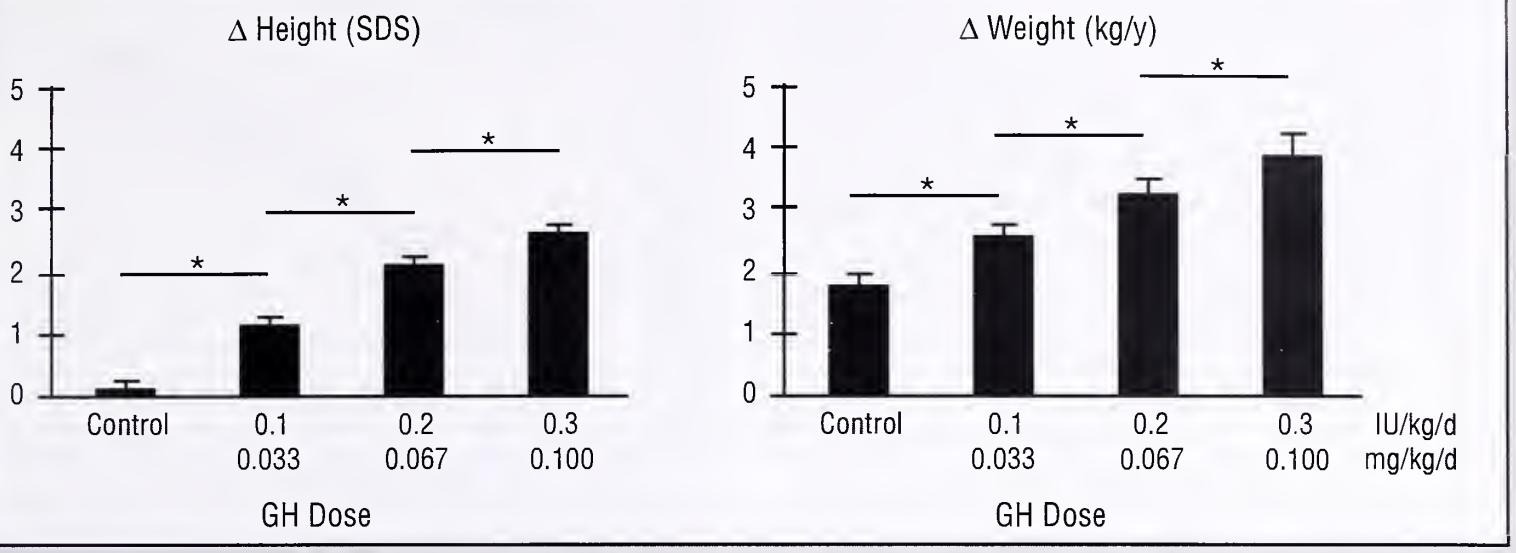
Figure 1



Evidence for "the critical window" phenomenon is demonstrated. Dotted lines indicate the average weight gain from birth in rats. Full lines represent the average weights of infant rats who were undernourished (noted by arrows) early in life or later (after 3 weeks). Permanent effects occur if undernutrition is present early, suggesting "a critical window of time" for a phenomenon to occur for subsequent adversity.

Adapted with permission from McCance RA, et al. *Proc R Soc Med (Lond)* 1962;156:326-337; Widdowson EM, et al. *Proc R Soc Med (Lond)* 1963;158:329-342.

Figure 2



GH-induced catch-up growth is demonstrated to be dose dependent. Epianalysis results of height and weight (means ± SEM) from 3 independent randomized controlled studies in short prepubertal SGA children without GHD who were treated with 1 of 3 doses of GH over 2 years are presented. * P=<0.01.

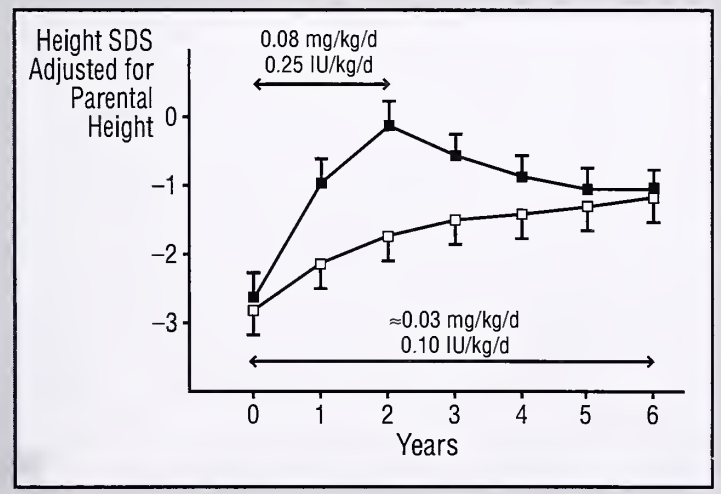
Adapted with permission from de Zegher F, et al. *Trends Endocrinol Metab* 1998;9:233-237.

Finally, we emphasize that to date, the different GH-treatment regimens applied to SGA children have a reassuring safety profile and do not lead to inappropriate acceleration of bone maturation or to disproportionate growth, eg, within the craniofacial complex.[12,14]

PRONOUNCED ADRENARCHE AND PRECOCIOUS PUBARCHE

Almost 80% of the fetal adrenal consists of the so-called fetal adrenal zone, which is located in the inner area of the cortex and which virtually disappears in early infancy. It has been known for 25 years that reduced fetal growth is associated with reduced size of the fetal adrenal zone and reduced concentrations of dehydroepiandrosterone sulfate (DHEAS) in fetal serum. "Adrenarche" refers to the endocrine process that results in rising serum concentrations of adrenal androgens produced by the zona reticularis within the inner part of the adrenal cortex. Adrenarche occurs normally between 6 and 8 years of age. "Pubarche" refers to the appearance of pubic hair. By definition, pubarche before the chronologic age of 8 years is considered to be precocious.

Figure 3



Two years of GH treatment at high dose (n = 13) produces the same ultimate growth 6 years later as 6 years of treatment at a lower dose (n = 14). The mean age at start of treatment was 4 years in these prepubertal SGA children.

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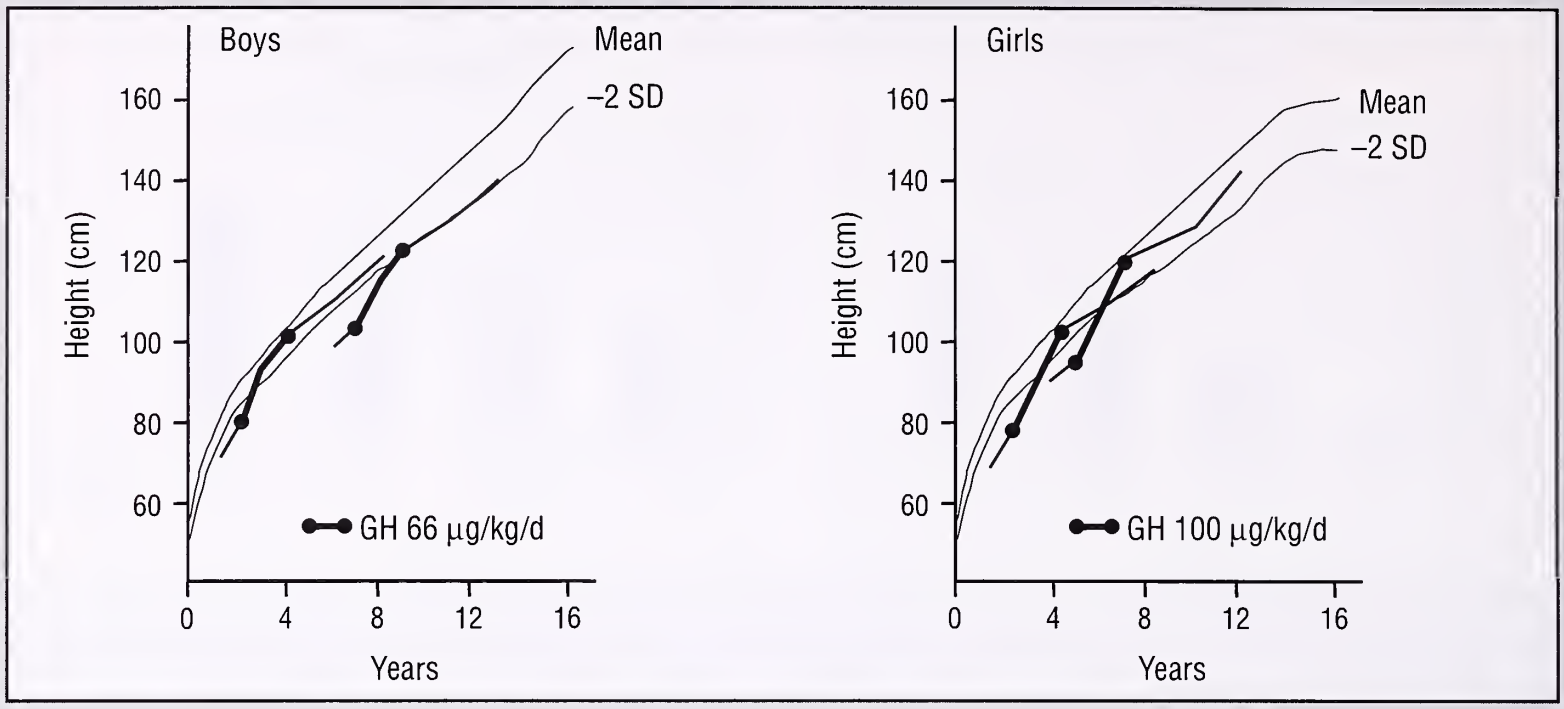
Two independent studies recently indicated that adrenarche is more pronounced in children born SGA as compared with appropriate-for-gestational age (AGA) controls, particularly if the SGA children had experienced spontaneous catch-up growth.[15,16] These biochemical findings are already becoming of clinical relevance as idiopathic precocious pubarche, a frequent clinical expression of early adrenarche, also has now been associated with reduced fetal growth (Figure 5, page 4).[17]

MALE PSEUDOHERMAPHRODITISM AND SUBFERTILITY, OVARIAN HYPERANDROGENISM AND ANOVULATION

The embryonic gonads play a crucial role in sexual differentiation. Subsequently, during fetal and neonatal life the human gonads present a high profile of secretory activity. In turn, this phase is followed by a decade of low activity under neuroendocrine inhibition, and then by gonadal hormone production and pubertal development, which leads to a fully reproductive status.

Figure 4



The growth curves of these 4 prepubertal children illustrate that marked catch-up growth during high-dose GH treatment for 2 years may be followed initially by catch-down growth over a few years, but subsequently by sufficient spontaneous growth to maintain height at a higher level than the original level.

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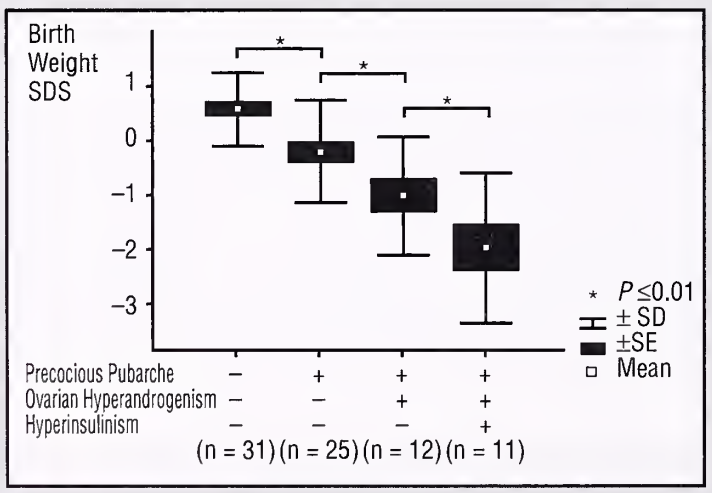
Androgen insensitivity, a form of male pseudohermaphroditism,[18] was found to result in a slightly reduced birth weight (–0.4 SD on average).[19] Even more intriguing is the recent finding that unexplained forms of male pseudohermaphroditism appear to be associated with a markedly reduced birth weight (–2 SD on average).[20]

Figure 5



The birth weights (SDS) of postmenarchal control girls are compared with postmenarchal girls having had precocious pubarche with or without ovarian hyperandrogenism (OH) and with or without hyperinsulinemia. The diagnosis of OH was based on the response of 17 hydroxyprogesterone to LHRH agonist. Hyperinsulinemia when demonstrated occurred during a standardized OGTT.

Adapted with permission from Ibanez L, et al. *J Clin Endocrinol Metab* 1998;83:3558-3562.

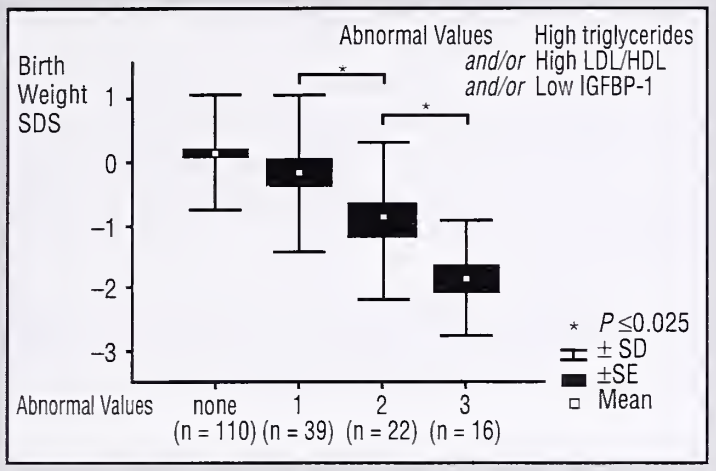
While reduced fetal growth has been associated with subsequent testicular dysfunction for half a century,[21,22] only recently has a specific link with male subfertility been recognized.[23] Reduced fetal growth is thought to be accompanied by an early decrease in the number and/or function of Sertoli cells, which, in turn, appear to be one of the key determinants of adult spermatogenesis.[23] Reduced fetal growth also has been associated with a reduced fraction of primordial follicles in fetal ovaries,[24] with ovarian hyperandrogenism in adolescent girls (Figure 5),[17] and with anovulation, particularly dating from late adolescence.[25] The timing of menarche and menopause, however, are quite independent of birth weight.[26,27]

DYSLIPIDEMIA AND INSULIN RESISTANCE

A few years ago, Barker et al identified the relation between reduced fetal growth and syndrome X in senescent men.[28] One of the mechanisms by which prenatal undernutrition may induce postnatal insulin resistance is by altering—within a critical window of time—the relative rates of multiplication of cells destined to form the perivenous and the periportal zones within the hepatic lobule, such that a relative but permanent excess of glucokinase and lack of phosphoenolpyruvate carboxykinase expression ensue.[29]

Asymptomatic insulin resistance has now been documented in SGA children with and without spontaneous catch-up growth, and is often detectable before

Figure 6



Birthweight SD scores of girls (age range 5 to 20 years) with (from left to right) either none, one, two, or all three of the following abnormal serum concentrations: high triglycerides, high LDL/HDL ratio, low IGFBP-1.

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puberty.[17,30] In the sequence of pediatric endocrinopathies linked to reduced fetal growth, insulin resistance was found to be associated with the lowest birth weights (Figure 5). In accord with the latter findings, reduced fetal growth also has now been linked to low serum IGFBP-1 concentrations, which are thought to reflect hepatic hyperinsulinism in children and adolescents. Hypertriglyceridemia and an increased serum low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio often occur (Figure 6), indicating that children and adolescents with SGA already tend to display an atherogenic lipid profile.[31]

CONCLUSION

There is increasing evidence that reduced prenatal growth is associated with a modulation in the function of multiple components within the postnatal endocrine system. A minority of children born SGA experience a persistent reduction of postnatal growth, which has been attributed to either classic or neurosecretory GHD and/or to some form of IGF-1 resistance. The short stature of most prepubertal SGA children can be normalized with a variety of GH treatment regimens; however, on average, a slightly higher than conventional dose seems to be required. Adrenarche appears to be amplified in SGA children, and idiopathic precocious pubarche has been associated with relatively low birth weights. Similar associations have been found for male pseudohermaphroditism and subfertility and for ovarian hyperandrogenism and anovulation. Finally, insulin resistance has been documented in both prepubertal and pubertal SGA children with and without spontaneous catch-up growth, and dyslipidemia also has been linked to reduced fetal growth. Thus, children born small appear to be at increased risk for experiencing endocrine and metabolic dysfunction; in addition, the lower the birth weight, the more prone the child seems to be to developing a broad spectrum of endocrine and metabolic anomalies (Figures 5 and 6). The challenge now is to identify the molecular and cellular mechanisms underlying the aforementioned associations so that more than merely symptomatic treatments can be designed. A new chapter in pediatric endocrinology has begun.

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Recognition of Children With Psychosocial Short Stature: A Spectrum of Presentation

The conclusion of Gohlke et al is that psychosocial short stature (PSS) should be considered in every patient with "idiopathic" growth hormone deficiency (GHD) or when growth hormone (GH) treatment is ineffective in a child with presumed GHD. Symptoms such as hyperphagia, abnormal eating habits, disturbed behavior, global developmental lag, enuresis, or encopresis should prompt consideration of PSS, especially when there is a possibility of associated sexual abuse, which is frequently present in patients with this symptom complex.

Forty of the 65 children studied were single family cases; however, 25 represented multiple cases within 12 families. In half of the families, the parents were divorced or separated. The educational and work background of the parents was usually in the lower and unskilled categories. Unemployment of fathers was significantly excessive.

Sex distribution was equal. A remarkable finding was that only 29% of full-term newborns had a birth weight >3,000 g. Twenty-one percent of all patients were premature (<37 weeks). Bone age was delayed by an average of 1.9 years. Body mass index was normal in all patients.

Fifty-four percent had eating problems, 42% behavioral problems, 26% encopresis, and 18% nocturnal enuresis; 12% urinated in inappropriate places or as an aggressive act. Many suffered physical abuse as well as psychological abuse. Bizarre eating habits, etc, were common in the physically abused. The authors noted that their data after assessment were very different from the data given in the physician referral letters; items such as hyperphagia, enuresis, and encopresis were not mentioned at all in referral letters but were often obtainable when inquiry was made.

Three case histories were presented that emphasized different important aspects of this syndrome. In case No.1, failure to respond to GH treatment as expected in a child with presumed GHD was present. GH insensitivity may be the presenting sign of PSS. In case No. 2, separation of the affected children with PSS from the abusing family did not result in catch-up growth. When this happens, an adverse environment should be looked for in the second home. In addition, some patients who have an adequate initial response to GH subsequently fail to grow at an appropriate rate for a child with GHD under treatment; when this occurs, PSS should be suspected. The authors emphasize that not all PSS patients have classic findings of PSS. Case No. 3 demonstrated that abuse cannot always be proven, although several features of PSS may be present.

In the discussion, emphasis is made that a detailed psychological history should be taken for hyperphagia, polydipsia, and hoarding or scavenging food in all children suspected of having GHD.

Gohlke BC, et al. *J Pediatr Endocrinol Metab* 1998;11:509-517.

Editor's comment: *This syndrome is underdiagnosed in most pediatric clinics. These 65 children with PSS presented over a 7-year period to the pediatric endocrine clinic at Great Ormond Street. This syndrome is much more common than most pediatric endocrinologists believe, and the diagnosis often is not made because the physician does not think of the possibility. In retrospect, I myself have missed the diagnosis several times, although I am considered an authority in the field. Exemplary is my misdiagnosing GHD initially but finally diagnosing PSS in presumed GHD children who were not responding to GH satisfactorily.*

This article is abstracted because of its importance and because clinicians dealing with short stature need to consider the syndrome, know its variations, and suspect its presence, particularly in children of low normal or low birth weight and in short children who come from disrupted homes.

Robert M. Blizzard, MD

Previous publications relating to PSS appearing in *Growth, Genetics, & Hormones* are listed immediately below.

Abuse or Psychosocial Dwarfism: An Update. 1985;1(4):1-4.

Physiological GH Secretion During the Recovery From PSS. A Case Report. 1989;5(2):14.

Psychosocial Growth Failure: A Positive Response to GH and Placebo. 1992;8(4):13.

Letter to and Letter from the Editor. 1993;4(1):9.

A New Stress-Related Syndrome of Growth Failure and Hyperphagia in Children Associated With Reversibility of GH Insufficiency. 1997;13(1):9-11.

A Prolactin-Releasing Peptide in the Brain

The investigators isolated a gene for a 7-transmembrane, G-protein-associated, orphan receptor, itself expressed primarily in the pituitary; they then transfected this receptor into Chinese hamster ovary cells and thereafter isolated 2 peptides from hypothalamic extracts that bound to this receptor and had specific prolactin-releasing activity. They identified the bovine, rat, and human genes coding for these peptides. The human gene encodes an 87 amino acid peptide with a 22 amino acid signal peptide, prolactin-releasing 31 amino acid (amino acids 23-53) and 20 amino acid (amino acids 34-53) peptides, and a carboxyl terminal 34 amino acid sequence. The carboxyl terminal glycine of both peptides must be amidated for full bioactivity. The prolactin-releasing activity of the 31 amino peptide (PrRP31) was comparable to that of thyrotropin-releasing hormone. This report also demonstrated the importance of the arachidonic acid signal transduction pathway in prolactin secretion, as it was this signal that was employed to monitor the isolation and identification of these peptides.

Hinuma S, et al. *Nature* 1998;393:272-276.

Editor's comment: *A specific prolactin-releasing substance to complement the prolactin inhibitory activity of dopamine has*

long been sought and now appears to have been isolated. The physiologic role of the prolactin-releasing peptides is unclear, and their diagnostic or therapeutic relevance remains to be assessed. The "reverse" process by which the prolactin-releasing peptides were found (ie, identification of an orphan receptor and then its ligands) indicates the revolution in biologic investigation in which we have the privilege of participating. Details concerning the lactotroph cell membrane receptor specific for the prolactin-releasing peptides are awaited. Meunier's comments and entire article (Nature 1998;393:211-212) *are exceedingly worthwhile reading.*

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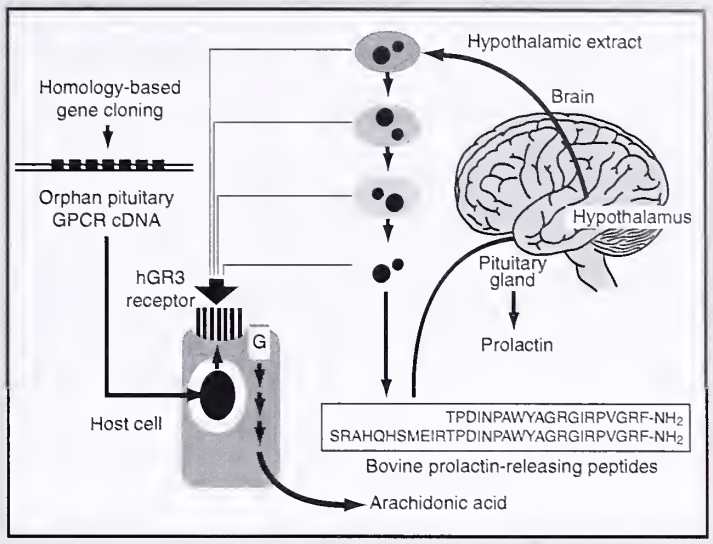

The strategy used by Hinuma et al to isolate and identify the prolactin-releasing peptides is schematized above. The components in the hypothalamic extracts that turned out to be the active ones (that is, promoted synthesis of arachidonic acid in recombinant host cells) are depicted as small and larger black circles. The sequences are those deduced from the primary structure of the precursor, the complementary DNA for which the authors also have cloned.

Reprinted with permission from Meunier J-C. *Nature* 1998;393:211-212.

GH Dependence and GH Withdrawal Syndrome in GH Treatment of Short Normal Children: Evidence From Growth and Cardiac Output

Lampit et al evaluated the efficacy of interrupted growth hormone (GH) therapy in prepubertal children with idiopathic short stature (ISS). Their protocol was to treat normal short children for a period of 3 years or until they reached the 25th percentile and then to discontinue therapy at a young age (no more than 9 years of age) and follow them until final height. The criteria for ISS were height <–2 SD, growth rate more than –1 SDS, bone age <75% of chronologic age, and serum GH concentration following arginine stimulation of >10 µg/L. Thirty-four children were studied, 12 of whom served as a control group. In addition to measuring the children, Doppler echocardiographic evaluation was performed before recombinant human GH (rhGH) therapy, yearly for 2 years during therapy, and at 6 and 12 months after the cessation of therapy.

The children receiving rhGH were treated until their height reached the 25th percentile but for no longer than 3 years, even if they had not reached this percentile. Nineteen of the children completed 3 years of rhGH therapy (0.9 mg/m^2 daily). During the first year of treatment, the growth velocity accelerated as expected. After withdrawal of rhGH, growth decelerated in every child over a 6-month period to a velocity that was significantly lower than pretreatment values. The growth velocity recovered to pretreatment values by the fourth semiannual measurement. Height SDS also increased in the treatment group and then declined somewhat in the second year of therapy. The GH response to arginine was not significantly different after rhGH therapy. Insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) remained unchanged throughout the study. However, systolic and diastolic parameters fell significantly during the initial 6 months of rhGH withdrawal and remained low for 12 months. Aortic cardiac output also fell significantly during the initial 6 months of rhGH withdrawal. No child had any symptoms referable to these cardiac changes.

The authors state that these data suggest that it may be feasible to interrupt rhGH prior to puberty in order to achieve an improved final height, but they will not know this for certain until the patients reach their final height. More interestingly, their report suggests that rhGH treatment is associated with the development of a physical adaptation to continuous high levels of GH. The rhGH withdrawal symptoms were not induced by alterations of serum GH or IGF-1.

Lampit M, et al. *Eur J Endocrinol* 1998;138:401-407.

Editor's comment: *This is a fascinating report. It has become more and more apparent that adults with GH deficiency (GHD) have significant improvement in cardiac function when they are restarted and maintained on replacement therapy. It would appear that the administration of rhGH to children who do not manifest GHD induces a dependency on rhGH for cardiac function.*

Indeed, when rhGH is interrupted there is a significant reduction in cardiac output. Although the authors state that there have been no clinical symptoms associated with the cardiac findings, the effect of either longer periods of rhGH administration or

withdrawal has not been studied. It would be of interest to repeat these studies periodically over several years before concluding that there are no permanent changes associated with the initiation and subsequent withdrawal of rhGH in normal short children.

William L. Clarke, MD

Quality of Life of Young Adults With Idiopathic Short Stature: Effect of Growth Hormone Treatment

The authors assess the quality of life (QOL) and well-being of 89 fully grown, young adults with idiopathic short stature (ISS), some of whom had been treated with recombinant human growth hormone (rhGH) (N=24, 16 males; 0.2 to 0.3 mg/kg/wk for 3.8 to 8.1 years) and others who had not (N=65, 40 males). They also compared the data for these subjects with data for the average Dutch population of similar age. The mean adult height for all ISS children was –2.35 SD. Except for a decrease in the number of rhGH-treated subjects with a partner, there was no difference between the rhGH-treated and nontreated subjects with ISS in educational attainment, state of general health, personality inventory, or psychosocial/employment difficulties encountered because of short stature. The adult heights of the 2 populations were similar. The rhGH-treated subjects achieved an adult stature that was 3.3 cm greater than the pretreatment predicted adult height (range, –9.9 to +13.4 cm); interestingly, the rhGH-treated individuals estimated their adult height to be 13 cm (range, 0 to 28 cm) greater than they would have reached without rhGH administration, a perception also shared by their parents. Although expressing a desire to be taller, when the rhGH-treated and nontreated ISS subjects were asked if they were willing to risk loss of longevity in order to achieve greater stature by taking a lifelong medication, or to risk loss of life by a height-increasing surgical procedure, only a minority (11% to 22%) indicated a willingness to do so. Most ISS subjects were satisfied with their heights. In comparison to the general Dutch population, there were no meaningful differences in QOL of the ISS subjects, whether treated with rhGH or not (see Table). The significance of the lower frequency of a partner in the rhGH-treated ISS subjects was unclear but not considered significant as it did not differ from the general Dutch population. The authors concluded that "the QOL of rhGH-treated and untreated young adults with ISS was similar and equal to the general population."

Rekers-Momberg LTM, et al. *Acta Paediatr* 1998;87:865-870.

Editor's comment: *These data indicate that: (1) subjects with ISS do not differ from taller peers in their QOL; (2) administration of rhGH does not meaningfully increase adult stature or improve the QOL of treated subjects; and (3) the perception of the effectiveness of rhGH in increasing height is vastly overestimated by the treated subjects and their families. In the experience of this physician, it is the concern of the parents rather than of the child who has been brought with ISS for pediatric endocrine consultation. It is essential that the pediatric endocrinologist confronted with the normal child with ISS fully inform the family about the limited expectations of therapy with rhGH on adult stature and future well-being, and emphasize the greater likelihood that the child's stature will have minimal impact on his function as an adult.*

Allen W. Root, MD

The Mean (SD) Values for Dimensions of the Dutch Restricted Version of the Minnesota Multiphasic Personality Inventory (NVM) for rhGH-Treated and Control Children With Idiopathic Short Stature (ISS)

Dimension of the NVM	Treated ISS (n = 17)	Controls ISS (n = 47)	Standard Population (n = 809)
Negativism	17.9 (10.3)	15.7 (9.7)	14.7 (7.7)
Somatization	5.9 (6.6)	4.7 (4.4)	5.3 (5.3)
Shyness	8.6 (7.5)	9.6 (7.6)	8.0 (6.4)
Severe psychopathology	3.1 (2.4)	2.7 (3.5)	2.7 (2.7)
Extroversion	20.4 (5.1)	19.7 (4.8)	17.1 (5.3)

Reprinted with permission from Rekers-Momberg LTM, et al. *Acta Paediatr* 1998;87:865-870.

Final Height After Combined Growth Hormone and Gonadotropin-Releasing Hormone Analogue Therapy in Short Healthy Children Entering Into Normally Timed Puberty

Controversy continues as to the feasibility of using gonadotropin-releasing hormone analogues (GnRHa) in combination with recombinant human growth hormone (rhGH) to increase final height by delaying puberty and slowing bone maturation in short non-growth hormone-deficient (GHD) children. Lanes and Gunczler evaluated the effect of 2½ years of

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5 = Excellent 4 = Above average 3 = Good 2 = Below average 1 = Poor

Please evaluate this course with respect to the following:

1. Educational value of newsletter	5	4	3	2	1
2. Clinical relevance of articles	5	4	3	2	1
3. Newsletter style/format	5	4	3	2	1
4. Length of articles	5	4	3	2	1
5. Were the educational objectives met?	5	4	3	2	1

6. In your opinion, how could this newsletter be improved?

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UNIVERSITY OF VIRGINIA
HEALTH SCIENCES CENTER
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GROWTH, Genetics, & Hormones
Volume 15, Number 1

Post-Program Self-Assessment/CME Verification
Answer Sheet

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combined rhGH and GnRHa therapy in 10 short children (7 girls, 3 boys) with a mean chronologic age of 11.8 ± 1.2 years, mean bone age of 11.2 ± 0.9 years, and mean height -2.4 ± 0.4 SD below the 50th percentile. These children had an initial mean predicted height of 150.7 ± 9.8 cm (target height, 160.7 ± 5.3 cm) and all were in Tanner stage-II puberty. The control group included 7 girls and 3 boys with a mean chronologic age of 11.4 ± 1.0 years, mean bone age of 11.0 ± 0.8 years, and mean height –2.3 ± 0.4 SD below the 50th percentile who were in Tanner stage-II puberty. They had a mean predicted height of 151.8 ± 10.1 cm (target height, 159.5 ± 5.1 cm). No subject had GHD as determined by responses to clonidine stimulation. The subjects in the study group received rhGH at a dose of 0.1 U/kg/d SC 6 days a week (0.2 mg/kg/wk) and GnRH (leuprolide acetate) at a dose of 0.3 mg/kg IM q28d. Subjects were treated for 30 ± 5.2 months.

As anticipated, combined therapy resulted in interruption of pubertal development. Growth velocity decreased from 6.5 ± 1.6 cm/y to 3.9 ± 1.3 cm/y during the second year of combined therapy, resulting in a height z-score reduction from –2.4 ± 0.4 to –2.6 ± 0.7 SD (see Figure). Bone age maturation declined as well, averaging 0.5 bone age year/year of treatment. Predicted final height improved slightly by 12 months, but at the end of treatment was similar to baseline. The predicted final height of the study population after 2 years of therapy was 150 ± 8.0 cm while that of the control population was 151.2 ± 9.4 cm. After the discontinuation of combined therapy, growth velocity did not improve but the bone age advanced more rapidly, averaging 2.0 ± 0.4 cm/y of follow-up. The mean final height of the study group was 151.7 ± 2.4 cm, not greater than the mean pretreatment predicted final height of 150.7 ± 9.8.

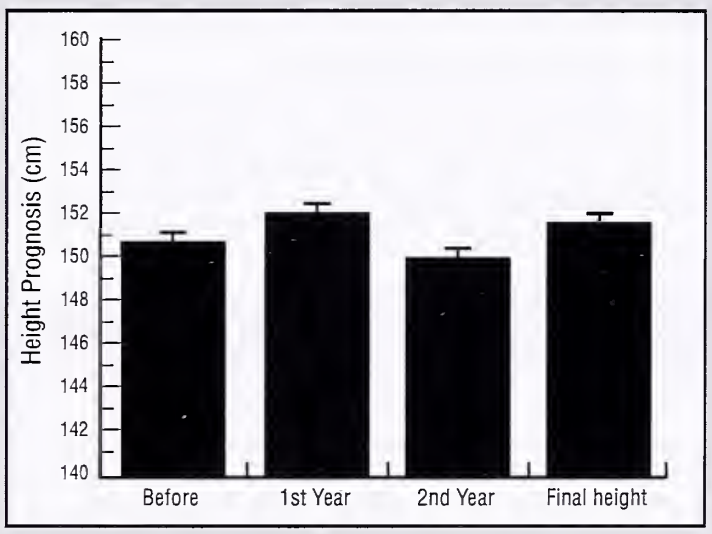
Lanes R, Gunczler P. *Clin Endocrinol* 1998;49:197-202.

Editor's comment: *Although this is a study of a relatively small number of subjects, the inclusion of a very well-defined control group strengthens the findings. In this particular study, it is very clear that the combined use of rhGH and GnRHa did not increase final adult height. Whether initiating therapy in children in slightly earlier stages of puberty or administering larger doses of rhGH might have resulted in a better outcome remains to be seen. The authors point out that this is only the second study that they know of following children receiving combined therapy to final height. The other study was conducted by Balducci and colleagues. The findings by Balducci's group produced similar results as reported by Lanes and Gunczler. These findings are important and should caution pediatric endocrinologists to be conservative in suggesting that such therapy may be of benefit to non-GHD short children who are entering puberty. Previously, several studies using GnRH alone were equally none productive.*

William L. Clarke, MD

Balducci L, et al. *J Clin Endocrinol Metab* 1998;80:3596-3600.

Predicted Adult Height Before and During Treatment and Final Height of Patients



Reprinted with permission from Lanes R, Gunczler P. *Clin Endocrinol.* 1998;49:197-202.

Morbidity in Turner Syndrome

This is a report using data from the Danish Cytogenetic Central Register and the Danish National Registry of Patients to assess the morbidity of women with Turner syndrome (TS) during the 10 years from January 1, 1984, to December 31, 1993. This study includes all women living in Denmark during that period. Five hundred ninety-four women with TS were identified. The observed number of diagnoses among TS patients was compared with the expected number calculated from the incidence in the study base. Not surprisingly, the relative risk of having an endocrine diagnosis, particularly hypothyroidism and thyroiditis, was much greater in women with TS than in the general female population (see Table). Insulin-dependent and noninsulin-dependent diabetes also were increased. Congenital malformations were most consistent among patients with 45,X karyotype. Osteoporosis and fractures occurred more frequently in women with TS, especially in the metacarpal bones and in the femoral neck. Fractures of the spine, ulna, and radius also were seen more frequently. The relative risk of cancer among women with TS does not seem to be elevated compared with the general population, except for cancer of the rectum and colon. In addition, women with TS had a significantly increased relative risk of heart disease, arteriosclerosis, hypertension, and vascular disease of the brain. Finally, the relative risk of cirrhosis of the liver was significantly elevated. As expected, the relative risk of endocrine diseases reached a maximum in the young age groups, while the relative risk of fractures reached a maximum in the older age group. The authors stress that women with TS have a risk profile similar to that of postmenopausal women.

Gravholt C, et al. *J Clin Epidemiol* 1998;51:147-158.

Editor's comment: *This is a very large and carefully performed epidemiologic study. The finding that women with TS have a relative risk profile similar to that of postmenopausal women suggests ways in which pediatric and adult endocrinologists might intervene to significantly alter this morbidity. In Denmark, it is suggested that most women with TS receive lifelong sex steroid replacement therapy. The specific age at which therapy is initiated remains somewhat controversial as pediatric endocrinologists attempt to maximize the height of these young girls. It is important, however, to stress to these young girls the importance of continuing therapy throughout adulthood as a possible protection against excess morbidity.*

William L. Clarke, MD

Relative Risk of Endocrine Diseases in Turner Syndrome

Diagnoses (ICD-8)	Observed	Expected	RR (95% CI)
Endocrine diseases, overall (240-258)	51	10.47	4.87 (3.63-6.41)
Thyroid diseases, overall (240-246)	10	4.98	2.00 (0.96-3.69)
Thyrotoxicosis (242)	3	1.50	2.01 (0.41-5.86)
Hypothyrosis (244)	3	0.52	5.80 (1.20-16.94)
Thyroiditis (245)	3	0.81	16.60 (3.42-48.50)
Insulin-dependent diabetes mellitus (249)	9	0.78	11.56 (5.29-21.95)
Noninsulin-dependent diabetes mellitus (250)	13	2.88	4.38 (2.40-7.72)
Miscellaneous endocrine diseases [251-258 (-251.13-15)]	15	1.72	8.71 (4.87-14.36)
Parathyroid disease (252)	1	0.14	7.25 (0.18-40.37)
Hypoglycemia (251.00)*	2	0.57	3.51 (0.43-12.69)

* Based on diagnosis on the 5-digit level.
CI, confidence interval
RR, relative risk

Reprinted with permission from Gravholt C, et al. *J Clin Epidemiol* 1998;51:147-158.

Growth Failure in Prader-Willi Syndrome Is Secondary to Growth Hormone Deficiency

Thacker and colleagues conducted a retrospective study of 16 children who met the diagnostic criteria for Prader-Willi syndrome (PWS). All had hypotonia during the neonatal and infantile periods, failure to thrive, rapid weight gain after the first year of life, dwarfism, hypogonadism, developmental delay, and hyperphagia. The 15q11-13 chromosomal abnormality had been identified in 13 of the 16. Growth hormone deficiency (GHD) as defined by growth hormone (GH) response <10 ng/mL on a provocative test was present in 12 of the 16. All the nonobese patients were GHD. Seven of the children were treated with recombinant human GH (rhGH) at a dose of 0.3 mg/kg/wk, and rhGH therapy continued for 6 to 23 months (see Table). All 7 children treated with rhGH had significant increases in their growth velocity. The authors state that although their study was retrospective, it suggests that the secretion of GH in PWS children is related to abnormalities of the hypothalamic-pituitary axis rather than to their obesity per se. This is based in part on the association of low insulin-like growth factor 1 (IGF-1) levels in most, which is not attributable to obesity, plus low GH responses to pharmacologic stimulation.

Thacker M, et al. *Hormone Res* 1998;49:216-220.

Annualized 6-Month Pretreatment and Posttreatment Growth Velocities (GV) in Prader-Willi Syndrome Children Treated With Recombinant Human Growth Hormone at a Dose of 0.3 mg/kg/wk

Patient No.	Pretreatment GV (cm/y)	Posttreatment GV (cm/y)
5	4.5	10.00
9	5.16	13.92
10	3.90	13.20
11	3.60	12.00
14	0.00	6.76
15	1.80	12.30
16	2.50	7.66

Reprinted with permission from Thacker M, et al. *Hormone Res* 1998;49:216-220.

Editor's comment: *This interesting report describes another clinical syndrome, PWS, in which GHD plays a major role. The children in the study were well characterized both by clinical and laboratory criteria. These investigators have made a worthy retrospective analysis of a potential etiology of GHD and rhGH treatment in PWS. The lack of a response to provocative stimuli and subsequent increases during rhGH therapy underscore the importance of evaluating these children when seen in the clinical situation.*

William L. Clarke, MD

Growth Hormone Treatment of Children With Prader-Willi Syndrome Affects Linear Growth and Body Composition Favorably

Lindgren et al studied 29 prepubertal children with Prader-Willi syndrome (PWS), all of whom had a paternal deletion or a maternal disomy of chromosomal region 15q11-13, hypotonia, hypogonadism, hyperphagia, obesity, short stature, psychomotor retardation, behavioral abnormalities, and dysmorphic features. In addition, 10 control healthy obese prepubertal children were studied. Growth hormone (GH) was sampled every 30 minutes for 24 hours and plasma insulin-like growth factor 1 (IGF-1), glycosylated hemoglobin, and fasting insulin and glucose were determined. Body mass and body mass index were calculated. Fat-free mass was determined by bioelectrical impedance and by dual energy X-ray absorptiometry. Fifteen of the 29 children with PWS were treated with GH at a dose of 0.1 IU/k/d (0.23 mg/kg/wk) SC for 1 year. The others served as a second control group.

The obese control children were tall and had normal increased serum IGF-1 levels, whereas the PWS children were short with normal or low IGF-1 levels. However, 24-hour GH secretion was low in both PWS and obese control children. During the 1 year of treatment, significant increases in height velocity were observed. Serum IGF-1 levels increased as well. Body mass index decreased and a 25% reduction in fat mass and a 30% increase in fat-free mass were observed. Fasting insulin levels increased significantly in the treated group, but fasting glucose and glycosylated hemoglobin levels were unchanged throughout the study. The authors state that these studies demonstrate that the majority of these patients were GH deficient and that GH deficiency is part of the hypothalamic dysfunction observed in this disorder.

Lindgren A, et al. *Acta Paediatr* 1998:87:28-31.

Editor's comment: *This description of the beneficial effects of GH in children with PWS supports those of Thacker et al recorded in the previous abstract. The children in the current study did not undergo stimulation tests, and thus their findings are not entirely biochemically comparable to those of Thacker et al. However, the growth responses of both groups were similar, and the additional finding of increased fat-free mass and decreased fat mass in the current study (Lindgren) demonstrates an additional important benefit of GH in these children.*

William L. Clarke, MD

Thacker M, et al. *Hormone Res* 1998;49:216-220.

Fathers and *FGFR3* Mutations

Achondroplasia is the prototype of short-limb dwarfism and is by far the most common form of dwarfism in humans. It results from activating mutations of the gene encoding fibroblast growth factor receptor 3 (*FGFR3*). The vast majority of cases result from new mutations, which in all cases involve nucleotide 1138 in exon 10 of this gene. This nucleotide is thus one of the most mutable nucleotides in the entire human genome.

The association of sporadic cases of achondroplasia with advanced paternal age has been recognized for years, suggesting that mutations at this site preferentially occur during spermatogenesis. The Wilkin group has now demonstrated this to be true.

Wilkin et al studied 97 families in which a child with achondroplasia had been born to parents of normal stature. They first identified a DNA polymorphism near the mutation site in the *FGFR3* gene. This enabled them to potentially determine if a mutation in a given case had occurred on the maternal or paternal *FGFR3* allele. The analysis was informative in 40 of the 97 families, revealing that the mutation occurred on the paternal allele in all 40 cases. In other words, the mutation had virtually always occurred in the *FGFR3* gene inherited from the father.

The authors discuss differences between spermatogenesis and oogenesis, noting that meiotic errors can accumulate to a much greater extent in the former because male germ cells divide much more often than do female germ cells. However, they acknowledge that the reasons why mutation of this particular nucleotide is so much more common during spermatogenesis are unknown.

Wilkin DJ, et al. *Am J Hum Genet.* 1998;63:711-716.

In Future Issues

Surfing the Web for Information on Genetic and Hormone Disorders

John A. Phillips III, MD

Editor's comment: *This paper confirms what has been suspected for years—that achondroplasia mutations of* FGFR3 *occur primarily, if not exclusively, during spermatogenesis. Unfortunately, the mechanism for the high rate of mutation in male germ cells remains obscure. The authors point out that the mutation occurs in the context of CpG dinucleotide, which is thought to predispose to mutation because of methylation and deamination of the G nucleotide. Other possibilities include defective repair of base mismatches that occur at this nucleotide during DNA replication, which for some reason occurs only during spermatogenesis. Another idea, which is pure speculation, is that such mutations adversely affect the survival of female germ cells so that only male germ cells harboring the mutation survive gametogenesis to contribute the mutations to offspring. It is interesting that recurrent mutations responsible for thanatophoric dysplasia occur in* FGFR3 *nucleotides that neighbor nucleotide 1138. This suggests that the underlying mechanism operates not just on the one nucleotide but also on the surrounding area, making it a very hot spot for mutation.*

William A. Horton, MD

2nd Editor's comment: *In* GGH *1997;13(4):49-54, Dr. Horton wrote an enlightening lead article entitled, "Molecular Genetics of Human Chondrodysplasias," which can profitably be read in conjunction with the abstract and editor's comments above.*

Robert M. Blizzard, MD

Celiac Disease and Turner Syndrome

The authors initially observed 2 of 26 patients with Turner syndrome (TS) who did not experience increased growth as expected when given recombinant human growth hormone (rhGH). These two GH-resistant patients were then diagnosed as having celiac disease (CD) antibodies, a characteristic of CD. Both patients had subtotal villus atrophy in the gastrointestinal tract, which confirmed the diagnosis. These findings stimulated screening of 35 TS girls, including the 26 receiving rhGH. Four of the patients, including the first 2, were anti-endomysium antibody (EMA) positive. However, 14 of the 35 patients were positive for antigliadin antibodies, suggesting an immunologic phenomenon seen in CD. The authors confirmed the high coincidence of TS and autoimmune thyroid disease in 6 of the 35 patients and overt hypothyroidism in 4.

The authors conclude that the results of the study indicate that gluten sensitivity may be an associated characteristic in TS, and that screening with EMA together with other autoantibodies is advisable in TS at least before starting rhGH treatment.

Bonamico M, et al. *J Pediatr Gastroenterol Nutr* 1998:26;496-499.

Editor's comment: *The association of autoimmune diseases, particularly thyroid autoimmune disease, has long been recognized. This is the first account known to me of the possible association of CD and TS and should be explored further.*

Robert M. Blizzard, MD

SHOX Mutations in Dyschondrosteosis

The *SHOX* story began about a year ago with the identification of a gene encoding a homeobox-containing transcription factor that maps to the pseudoautosomal region of the X chromosome. The detection of a missense mutation predicted to truncate the protein in a short child suggested that it or, more appropriately, its absence may play a role in the short stature of Turner syndrome (TS). The story has taken a new turn with the finding of *SHOX* mutations and deletions in patients with dyschondrosteosis (DCS).

DCS, or Leri-Weill syndrome, is a relatively mild dwarfing condition that mainly involves the middle segments of the limbs. The major features are shortening of the lower legs and bowing of the radius associated with the Madelung deformity of the wrist. DCS occurs in both males and females and is usually more severe in females. Its inheritance has been considered autosomal dominant based on several examples of male-to-male transmission. In fact, it has long been suspected that the much more severe condition, Langer mesomelic dysplasia, results from homozygosity for DCS.

Two independent groups, Belin et al and Shears et al, carried out very similar studies. Starting with several large families exhibiting dominant transmission of DCS, both groups first established linkage of DCS to gene markers near the *SHOX* locus. Belin et al also linked DCS to a marker within the *SHOX* gene. Next, both groups detected deletions of the *SHOX* gene in DCS patients; Belin and colleagues found deletions in 7 families and Shears and colleagues had detected deletions in 5 families. Finally, point mutations were found in 2 families that segregated with the DCS clinical phenotype. Both groups concluded that the DCS phenotype results from haploinsufficiency for the *SHOX* transcription factor since patients were either missing 1 *SHOX* allele or had mutations predicted to make the transcription factor nonfunctional.

Both groups also provided evidence that Langer mesomelic dysplasia results from the homozygous loss of *SHOX* function. Langer mesomelic dysplasia had been suspected clinically in an infant with 45,XO TS in 1 of the studies by Belin's group. Molecular studies showed that this patient had no *SHOX* alleles; she inherited an X chromosome harboring a *SHOX* deletion

from her mother and lacked a paternal X or Y chromosome. In the other case, a fetus appeared to inherit an X chromosome deleted for *SHOX* from the mother and a Y chromosome with an abnormal *SHOX* gene from the father.

Both groups acknowledge that there are still many unanswered questions, including why DCS is usually more severe in females than males and why the Madelung deformity occurs in some families and not in others.

Belin V, et al. *Nature Genet* 1998;19:67-69.
Shears DJ, et al. *Nature Genet* 1998;19:70-73.

Editor's comment: *This article brings out several important points. For instance, it delineates the molecular genetics of DCS and probably of Langer mesomelic dysplasia. It provides further insight into the short stature of TS. It also illustrates that male-to-male transmission of a trait does not always indicate autosomal dominant inheritance. In this case, it indicated what might be called "pseudoautosomal" inheritance.*

The 2 point mutations were interesting. First, they are very close to one another, converting arginine 195 and tyrosine 199 to stop codons. The protein products are predicted to truncate the protein downstream of the DNA-binding homeobox domain. It is not surprising that such mutations would produce similar clinical phenotypes. Second, the arginine 195 mutation was the same mutation observed in a family with "idiopathic short stature" in the original report of the SHOX *gene by Rao et al. This implies that the clinical phenotype of DCS can blend into that of idiopathic short stature. Alternatively, the DCS features may have been so mild as to escape detection in the original family. It will be important to determine which is the case. If it is the former, screening for* SHOX *mutations may become an element in the workup of idiopathic short stature.*

These reports do not fully resolve the issue of whether short stature in TS is caused by dysfunction of 1 gene, SHOX*, or more than 1 gene. However, the presence of the Madelung deformity is not an uncommon feature of TS, and suggests that disturbance of* SHOX *function plays an important role in the pathogenesis of this syndrome.*

William A. Horton, MD

Rao E, et al. *Nature Genet* 1997;16:54-63.

Teratogen-Mediated Inhibition of Target Tissue Response to *Shh* Signaling

In the mouse in which Sonic hedgehog (*Shh*) is knocked out, there is severe holoprosencephaly, a developmental anomaly associated with abnormal formation of the brain, eyes, optic nerves, and pituitary. Covalent binding of cholesterol to Shh protein is essential for its normal processing and functioning. Experimentally, administration of agents that inhibit cholesterol synthesis to pregnant rats led to holoprosencephaly in their offspring. The present investigators demonstrated that administration of the plant alkaloid jervine, a compound that is structurally similar to cholesterol and inhibits terminal steps of cholesterol synthesis, causes holoprosencephaly in chick embryos with failure of separation of paired midline structures. In vitro in explant cultures of medial neural plate from chick embryos, addition of jervine inhibited Shh signaling; similar findings were observed when other inhibitors of cholesterol synthesis were examined in this system. However, further studies revealed that these agents did not inhibit normal processing of Shh, although the generated product was unable to induce signaling. The investigators suggest that in addition to inhibition of cholesterol biosynthesis, these compounds may block normal cholesterol movement within cells and interfere with Shh-associated proteins that interact with Shh in the intracellular signaling pathway that leads to normal morphogenesis. Thus, cholesterol is important for both proper preparation of Shh for its signaling function *and* for the cellular response to Shh.

Cooper MK, et al. *Science* 1988;280:1603-1607.

Editor's comment: *In humans with loss-of-function mutations of* Shh*, variable forms of holoprosencephaly occur, the most extreme of which is cyclopia (a single large eye) and the mildest fused central incisor teeth. In patients with the Smith-Lemli-Opitz syndrome associated with mutations in 7-dehydrocholesterol reductase, mild forms of holoprosencephaly occur. The clinical and experimental data indicate that cholesterol influences developmental signaling pathways. In target cells, Patched is a protein that binds to and is necessary for Shh signaling; Patched contains a cholesterol recognition domain. It has been hypothesized that if a cell is deficient in cholesterol, Patched may not bind to Shh and the signaling pathway is then arrested. Whether these observations bear on the optimal amount of cholesterol that a pregnant woman should ingest is unknown at present.*

Allen W. Root, MD

Straus E. *Science* 1998;280:1528-1529.

Target Height as Predicted by Parental Heights in a Population-Based Study

The authors examined the relationship between the adult stature of 2,402 normal Swedish young adults and that of their parents. As anticipated, there were strong correlations between the heights of the offspring, their parents individually, and particularly their midparental heights (average of mother's height + father's height, r=0.59). In further analysis of these data, the investigators determined equations for calculation of target heights for males and females based on midparental heights that were valid through a range of parental heights. The equations were:

Males: target height = 45.99 + (0.78 × midparental height)
Females: target height = 37.85 + (0.75 × midparental height)

The 95% predicted interval was ±10 cm. When the midparental height was shorter than –2 SDS, these equations overestimated target height by +2 cm. The authors also reported that there was little intergenerational (ie, secular) difference in adult stature (+0.7 cm males, +1.0 cm females), and that even major differences between the heights of the parents did not affect the validity of the equations. The investigators conclude that these equations are to be preferred over the Tanner formulation because they lead to less variation in calculated target height, particularly in very short subjects in whom growth-promoting therapy is to be evaluated.

Luo ZC, et al. *Pediatr Res* 1998;44:563-571.

Editor's comment: *These data need to be confirmed in other populations, particularly those in which a secular trend toward increasing stature persists. Although knowledge of the target height is useful as a therapeutic goal, the range of ±10 cm is still extraordinarily wide. The development of a highly accurate and reliable method to predict adult stature of the untreated short child would be an even more useful advance.*

Allen W. Root, MD

Metabolic Basis of Dysmorphogenesis: Smith-Lemli-Opitz Syndrome

The Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive inborn error of morphogenesis. The clinical phenotype includes craniofacial, digital, genital, and visceral abnormalities; microcephaly; mental retardation; and growth deficiency. Elevated levels of 7-dehydrocholesterol (7-DHC) have been found in SLOS patients. Since 7-DHC is the immediate precursor of cholesterol, deficiency of the enzyme responsible for the conversion of 7-DHC to cholesterol, Δ7-sterol reductase, has become a prime candidate mechanism to explain SLOS. Earlier this year, the group headed by Fabian Moebius cloned the cDNA encoding the catalytic subunit for this enzyme. Now they report the cloning of the gene, its mapping in humans to chromosome 11q13, and the identification of mutations in 13 patients with SLOS. Two other groups, working independently, have described mutations in the Δ7-sterol reductase gene in an additional 6 SLOS patients, bringing the total to 19 patients.

As noted in a review by Kelley, 19 different mutations (mutant alleles) have been found to date. Thirteen are missense mutations, 1 is a nonsense mutation, and 5 are frameshift mutations. One mutation, a 134-bp insertion, was found in more than 1 patient. All mutations are predicted to cause loss of enzyme activity; and Fascia et al demonstrated reduced synthesis of enzyme compared with normal for 5 of the missense mutations.

The mechanism by which the biosynthetic block disrupts normal morphogenesis is addressed mainly by Kelley. He points out that in addition to the direct effects on morphogenesis of excessive 7-DHC and deficient cholesterol, the latter may disturb signaling through hedgehog morphogens. This is because cholesterol is added to sonic hedgehog and probably other hedgehog proteins during their normal processing. The cholesterol mediates attachment of the proteins to the surfaces of nearby cells, thereby restricting their diffusion and consequently their effects on morphogenesis.

Fascia BU, et al. *Proc Natl Acad Sci USA* 1998;95:8181-8186.
Waterham HR, et al. *Am J Hum Genet* 1998;63:329-338.
Wassif CA, et al. *Am J Hum Genet* 1998;3:55-62.
Kelley RIL. *Am J Hum Genet* 1998;63:322-326.

Editor's comment: *The recent advances in molecular genetics have provided exciting insights into the molecular basis of genetic diseases. However, it is not uncommon to learn of a molecular defect but still not understand how it produces the clinical phenotype. This series of papers is commendable because they go beyond the description of the genetic and even protein defect to put forth a mechanism to explain the pathogenetic actions of the defect.*

It is ironic, as pointed out by Kelley, that despite the insights provided by these papers, the mainstay of diagnosis will continue to be measurement of biochemical parameters, such as 7-DHC, because they predict clinical severity and because the diversity of mutations makes them difficult to detect. Finally, it is noteworthy that anecdotal evidence suggests patients with SLOS improve substantially when their cholesterol deficiency is treated.

William A. Horton, MD

Growth in Children With Craniopharyngioma Following Surgery

Tiulpakov et al attempted to determine why some children rendered growth hormone deficient (GHD) secondary to surgery for craniopharyngioma continue to grow normally postoperatively. Twenty-five patients (14 boys, 11 girls), aged 3.8 to 18.9 years, were studied between 0.5 and 10.0 years after surgery. At the time of the study 22 were receiving thyroxine replacement, 13 glucocorticoid replacement, and 23 desmopressin for diabetes insipidus. None were receiving growth hormone (GH) or sex steroids. All children were prepubertal height. Height velocities were recorded as SDS values. Body mass index (BMI) and bone ages also were determined. Following an overnight fast, insulin-like growth factor 1 (IGF-1), IGF-binding protein 3 (IGFBP-3), IGFBP-1, and prolactin were measured. In addition, GH was measured following stimulation with oral clonidine and after 1 mg/kg GH-releasing hormone (GHRH) intravenously. Serum insulin levels were measured during an oral glucose tolerance test (OGTT).

Height SDS for chronologic age ranged from –4.7 to 0.6. However, 4 of the patients had height SDS values (–1.8 to –1.2) that were within normal limits. Height velocity for chronologic age in the patients under 12 years of age ranged from –4.5 to 8.4. BMI ranged from 14. 5 to 38.3, and there was a significant correlation between BMI and height SDS (r=0.37, P=0.03), but not between BMI and height velocity SDS. Thirteen patients showed hyperinsulinemia during OGTT. Only 2 of the 25 children had significant GH responses to oral clonidine with peaks >1.0 µg/L. Maximal GH after GHRH was < 5 µg/L in all but 1 subject. Mean fasting IGFBP-1 was 104.5 ± 53.7 µg/L. Only 8 of 31 measurements of fasting IGF-1 were within normal limits. IGF-1 SDS correlated significantly with both height SDS (r=0.77, P=0.0002) and bone age SDS (r=0.5, P=0.03). Fasting IGFBP-3 levels were within the normal range for 12 subjects and correlated significantly with height SDS, but not with height velocity SDS. IGFBP-3 SDS correlated significantly with the log of the insulin area under the curve (AUC) (r=0.56, P=0.002). Basal prolactin concentrations were slightly elevated in 5 subjects. Forward stepwise regression analyses of height SDS and height velocity SDS were performed. The following variables were included in the initial model: log time after surgery; tumor location; log BMI; midparental height SDS; log insulin AUC; log GH level after clonidine; log GH after GHRH; prolactin; IGFBP-1; IGFBP-3 SDS; and IGF-1 SDS. IGF-1 SDS was the single most important predictor for height SDS (r=0.33, P=0.001), while log time after surgery was most strongly associated (negatively) with height velocity SDS.

The authors note that the correlation between height SDS and BMI shows that obese subjects maintain a higher growth rate after surgery than nonobese patients. Hyperprolactinemia and hyperinsulinemia and normal IGF-1 were the most frequent findings in the fast-growing GHD patients. However, the correlation between log of insulin AUC and height SDS indicates that hyperinsulinemic patients maintain higher integrated growth rates after surgery compared with children with low or normal insulin. Significant correlations between the insulin AUC and IGF-1 SDS and IGFBP-3 SDS were observed. The authors concluded that the growth phenomenon in children following craniopharyngioma usually accompanied by obesity is likely to be associated with IGF-1 bioavailability, which may be modulated by insulin.

Tiulpakov AN, et al. *Clin Endocrinol* 1998;49:733-738.

Editor's comment: *This study of a relatively large number of individuals provides further information concerning the growth of children following craniopharyngioma surgery. The data are particularly interesting since not all of the 25 patients grew and since a large amount of data were examined. The fact that IGF-1 SDS was the single most important predictor of height SDS is not surprising. That IGF-1 levels might be modulated largely by insulin supports clinical observations. Pediatric endocrinologists need to continue to keep careful records with regard to auxologic and hormonal changes that occur in their patients following craniopharyngioma surgery. It would be of particular interest to know whether obese children remain obese once GH therapy is initiated and what changes occur in their growth velocity during that therapy.*

William L. Clarke, MD

Post-Program Self-Assessment/CME Verification

Instructions: The Post-Program Self-Assessment/Course Evaluation Answer Sheet can be found on the center page of the issue. Please follow the instructions listed there to receive CME Category 1 credit.

1. The concept presented in this article is:
   a) IUGR infants usually have gross chromosomal defects.
   b) SGA infants usually do not catch up in their growth until late childhood.
   c) Increased prenatal growth is usually a genetic or metabolic defect.
   d) Reduced prenatal growth frequently is related to a postnatal endocrinopathy.
2. Approximately ____ of infants as defined in this article are SGA.
   a) 10%
   b) 3%
   c) 1%
   d) 5%
3. This percent of infants is in accord with most definitions of SGA in the literature.
   a) Yes
   b) No—10% of newborns are usually included as being SGA by definition
4. SGA infants often catch up with normal infants in respect to auxology. ____ are usually in the normal range by ____ years of age in respect to height.
   a) 90%/2 years c) 60%/8 years
   b) 70%/5 years d) 50%/10 years
5. Which of the following features are stated to often be associated with SGA?
   a) An increased incidence of GHD
   b) Hyperandrogenism
   c) Insulin resistance
   d) Addison's disease
   e) Reduced testicular function

Answer Key: 1. d 2. b 3. b 4. a 5. a, b, c, e

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Disclosure: As mandated by the ACCME, all faculty participating in continuing medical education programs sponsored by the University of Virginia School of Medicine are expected to disclose to the program audience any real or apparent conflicts of interest related to the content of their presentation.

Drs. de Zegher, Francois, Ibanez, Lifshitz, Clarke, Horton, and Hall report no conflicts. Dr. Root serves on Genentech Corporation's National Cooperative Growth Study Advisory Committee. Dr. Blizzard is President of The Genentech Foundation for Growth and Development, which functions independently of Genentech, Inc.

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Surfing the Net for Information on Genetic and Hormone Disorders

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INTRODUCTION

New findings are reported at an ever increasing rate in a growing variety of journals. Access to current information on clinical and laboratory findings and on who performs genetic tests cannot be found in a single journal or text. Electronic databases are now providing medical professionals rapid access to a wealth of current information and data. These electronic databases can be searched in an interactive way for symptoms and signs that permit generation of differential diagnoses that will often include rare or recently discovered disorders and that professionals probably have never encountered. This access enables these professionals to diagnose cases more frequently and be aware of the subtleties that differentiate alternative diagnoses. These are excellent reasons to use electronic databases. This article attempts to enlighten interested professionals on how to surf the Net for information about genetic and hormone disorders.

ONLINE MENDELIAN INHERITANCE IN MAN

The Online Mendelian Inheritance in Man (OMIM) electronic database is maintained by the National Center for Biotechnology Information, or NCBI.[1] It is available without charge at http://www.ncbi.nlm.nih.gov/omim. It is updated daily. As of March 1999, 10,227 entries were included. A wealth of information is presented on the history, signs, symptoms, diagnosis, and management of, and research findings on, these 10,227 disorders, as are detailed gene and disease-focused maps. Access through "hyperlinks" to a variety of Web sites is another important strength. These hyperlinks include MEDLINE™, the Alliance of Genetic Support Groups, the Cardiff Human Gene Mutation Database (HGMD), and databases on genes that cause retinal diseases, mitochondrial diseases, and a variety of other locus-specific databases. The utility of using these databases and their hyperlinks in clinical applications is discussed below.

FREQUENTLY USED TERMS RELATED TO THE WEB

Knowing the definitions of terms helpful in using the Web is essential as a first step in surfing the Net.[2]

E-mail: An acronym for electronic mail; the use of a network to send and receive messages.

HTML: Acronym for hypertext markup language, which enables authors to insert hyperlinks. Clicking on a hyperlink displays another HTML document. Therefore, in a hypertext system, one can navigate by clicking on hyperlinks, which produces a display of another document that also contains hyperlinks.

Http: The Internet standard supporting exchange of information on the World Wide Web. Http enables the embedding of hyperlinks in Web documents. Http defines the process by which a Web client uses a Web browser program to originate a request for information

In This Issue

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and send it to a Web server, which is a program designed to respond to Http requests and provide the desired information.

Hypertext: A computer text form that allows readers to click on hyperlinks to display another document that also may contain hyperlinks to still other documents.

Internet: The worldwide system of linked computer networks that facilitates data communication services such as remote log on, file transfer, E-mail, the World Wide Web, and news groups. The Internet assigns every connected computer a unique Internet address so that any 2 connected computers can locate each other on a network and exchange data.

Log on/Log off: The processes of establishing (log on) and terminating (log off) a connection with a network or computer.

Netscape Communicator™: A package including a popular Web browser called Netscape Navigator™ that is available for Microsoft Windows™, Macintosh™ computers, and a variety of Unix™ workstations.

Online information service: America Online™ (AOL) is a for-profit firm that makes current news, stock quotes, and other information available to subscribers over standard telephone lines.

Surfing the Net: Exploring the World Wide Web by following a series of links of interest to the surfer.

URL: Acronym for uniform resource locator. On the Web, URLs are strings of characters that precisely identify an Internet's resource types and locations. The following *fictitious* URL identifies a Web document (http://www.genetic.edu). (1) (http://) indicates the domain name of the computer on which it is stored; and (2) (www.genetic.edu) fully describes the document's location. *In addresses*, small letters (www and http) are used. *In abbreviations not pertaining to addresses*, capital letters may be used (WWW and Http or HTTP).

Web (World Wide Web, or WWW): A global hypertext system that uses the Internet-linked computer network to facilitate data communication.

Web browser: A program that runs on an Internet-connected computer and provides access to the World Wide Web.

Web server: A program that accepts Http-formatted requests for information. The server processes these requests and sends the requested document.

Web site: A set of related documents making up a hypertext presentation on the World Wide Web. A Web site usually has a welcome or home page that serves as the initial document.

GENERATING DIFFERENTIAL DIAGNOSES FOR A DYSMORPHIC NEWBORN

Some form of dwarfism is suspected in a newborn. Ventriculomegaly and short limbs, as detected by fetal ultrasound, were noted at 20 weeks gestation. Chromosome studies based on amniotic fluid revealed a 46,XY pattern with no abnormalities noted. The fetal head size at 30 weeks gestation as noted on ultrasound was stated to be 35 weeks. The ventriculomegaly had resolved, and the limb lengths were those expected for a 29-week fetus. Physical examination detected macrocephaly, macroglossia, downward slanting palpebral fissures, cataracts, and syndactyly of the second and third fingers. Blood glucose was low at 28 mg/dL.

The attending neonatologist believes the baby "looks funny" and wants to know if you, the consultant physician, think the baby has a syndrome. He wants to know if the infant has this syndrome, how to confirm it, and what is the expected prognosis.

You as the consultant physician are unaware of this constellation of clinical findings and/or what syndrome might be present but must solve the problem. A ***keyword search*** is desirable. Since the World Wide Web might contain helpful information, one needs to initiate a search beginning with the OMIM database. The computer in the nursery is turned on and you or the operator opens Netscape Communicator, America Online, or whatever Web browser the computer has, and type in the OMIM URL or address–http://www.ncbi.nlm.nih.gov/omim. The OMIM home page appears on the computer screen and you click on "Search the OMIM Database," and then enter "macrocephaly" as a search term and press the "enter" key. Eighty-one disorders in the OMIM database have macrocephaly listed. This is too many items to consider, so you repeat the search using "cataract" as a finding, and 183 matching entries appear. This number of disorders is impossible to consider, so you search by using "syndactyly." The search produces 168 matching entries–again too many. A decision is then made to find out how many disorders have both macrocephaly and cataract by typing in both macrocephaly and cataract (macrocephaly AND cataract) as a search string. Only 7 entries are listed as having both of these findings. These are (1) #109400 Basal Cell Nevus Syndrome, BCNS; (2) #30700 Hydrocephalus Due to Congenital Stenosis of Aqueduct of Sylvius, HSAS1, HSAS, HYCX; (3) #301050 Alport Syndrome, X-Linked, ATS; (4) #156550 Kniest Dysplasia; (5) *231680 Glutaricaciduria IIA; (6) #312870 Simpson Dysmorphia Syndrome, SDYS; and (7) *231675 Glutaricaciduria IIC. The entry num-

CME CERTIFICATION

The *GGH* Editorial Board is pleased to announce Category 1 credit for *GROWTH, Genetics, & Hormones* from the University of Virginia School of Medicine. This enduring material has been planned and produced in accordance with the ACCME Essentials.

Overview: This enduring material is designed to provide physicians and other health professionals with current research and clinical information essential to providing quality patient care to children with growth problems and genetic disorders.

Target Audience: This enduring material is designed for pediatricians, pediatric endocrinologists, pediatric geneticists, and family medicine physicians interested in pediatric growth, genetics, and endocrine issues.

Method of Physician Participation: Physicians can study each issue of *GROWTH, Genetics, & Hormones*, respond to the post-test self-evaluation questions, and request CME credit for each issue. The estimated length of time to complete this enduring material is 1 hour.

Learning Objectives: Through participation in this enduring materials series, the participant will have the opportunity to:

1. Apply current research and advances to the management of patient care for optimum clinical outcomes.
2. Utilize current research and clinical care issues to initiate discussions with colleagues with a focus toward increased awareness of current issues and controversies.
3. Conceptualize areas for future research in the field of growth and genetics.

bers are in hypertext (color) on the screen, and clicking on the number will open each corresponding entry. To further focus, you add "syndactyly," entering macrocephaly and cataracts and syndactyly as a search string. Only 1 OMIM entry is listed for all 3 of these findings–#312870 Simpson Dysmorphia Syndrome, SDYS.

You have participated in a remarkable accomplishment. In less than 2 minutes, a large electronic database of genetic disorders was searched and a successive series of progressively refined differential diagnoses was generated. Open the matching file (#312870 SDYS)[3] by clicking your mouse on it, and the first page of information appears on the screen for review (Figure 1, page 20). The clinical synopsis under Table of Contents or the complete text of this entry can then be reviewed. Figure 1 is only the first of 7 pages of information on SDYS. Note in Figure 1 that the Database Links below the Table of Contents provide immediate access to other databases, including MEDLINE™. The diagnosis needs to be confirmed, and the HELIX™ database is a directory of laboratories that provide testing for genetic disorders (see list of selected Web sites on page 21). You register with HELIX and are given a password for professional users. This is used first to access and search the HELIX database for SDS or SDYS or the Simpson-Golabi-Behmel syndrome, and then to find matching labs that provide either clinical or research testing for this disorder. In a matter of a very few minutes, you have generated a working diagnosis (SDYS) and obtained information concerning the pathogenesis, mode of inheritance, and the findings associated with SDYS and access to a lab that can help confirm the working diagnosis. Obviously, after expending just a few minutes one feels much better prepared to talk with the neonatologist and the baby's parents, who are waiting for your opinion.

GENERATING DIFFERENTIAL DIAGNOSES FOR A FAMILY HAVING UNUSUAL ENDOCRINE PROBLEMS

A 15-month-old male is referred to you by his pediatrician, who suspects he has growth hormone deficiency. The child weighed 3.2 kg at full term following an uncomplicated pregnancy, labor, and vaginal delivery. The height SDS is now -3.2, and the length since age 5 months has become progressively retarded. The child is proportionate and the height and weight are commensurate with each other. The extremities appear normal in length, and no kyphosis, limitation of joint motion, or dysmorphic features are present. His bone age is delayed by more than -2 SD. You see no skeletal abnormalities. Serum thyroxine is abnormally low, but the electrolytes, glucose, urea nitrogen, bicarbonate and anion gap, calcium, phosphorus, and urine pH are all within normal limits. A 16-year-old full sister reportedly received growth hormone (GH) for presumed panhypopituitarism. The blood tests on the 15 month old reveal low serum levels of gonadotropins and thyroxine. Combined pituitary hormone deficiency is logical, as there is no response to GH-releasing hormone, thyrotropin-releasing hormone, and luteinizing hormone-releasing hormone, and the magnetic resonance imaging study reveals a hypocellular pituitary.

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Figure 1
OMIM Page Showing the First of 7 Pages of Information on Simpson Dysmorphia Syndrome. Note Database Links Below Table of Contents That Provide Immediate Access to Other Databases, Including MEDLINE.

OMIM Home | Search | Comments

#312870 SIMPSON DYSMORPHIA SYNDROME; SDYS

Alternative titles; symbols

BULLDOG SYNDROME
DYSPLASIA GIGANTISM SYNDROME, X-LINKED; DGSX
GOLABI-ROSEN SYNDROME
SIMPSON-GOLABI-BEHMEL SYNDROME; SGBS
SGB SYNDROME

TABLE OF CONTENTS

- TEXT
- REFERENCES
- CONTRIBUTORS
- CREATION DATE
- EDIT HISTORY
- CLINICAL SYNOPSIS

Database Links

MEDLINE | PROTEIN | DNA | Genome
Gene Map | Coriell | Nomenclature

Gene Map Locus: Xq26

Note: pressing the symbol will find the citations in MEDLINE whose text most closely matches the text of the preceding OMIM paragraph, using the Entrez MEDLINE neighboring function.

TEXT

A number sign (#) is used with this entry because of evidence that the Simpson-Golabi-Behmel overgrowth syndrome is caused by mutations in the gene for glypican-3 (300037).

In 2 males, sons of sisters, Simpson et al. (1975) observed a 'new' dysmorphism with the following features: broad stocky appearance, distinctive facies (large protruding jaw, widened nasal bridge, upturned nasal tip), enlarged tongue, and broad, short hands and fingers. Intelligence was normal. The family referred to the appearance as 'bulldog'-like. In infancy hypothyroidism was suggested, but this was excluded by laboratory tests. Close linkage with the Xg blood group locus was excluded. Kaariainen (1981) told me of a tall (192 cm) 40-year-old man with operated pectus excavatum, ventricular septal defect, central cleft of the lower lip, peculiar cup-shaped ears with knobbiness and nodularity, short clubbed terminal phalanges, low-pitched voice, and cataracts developing at age 35. The parents, who came from different parts of Finland, were 170 and 160 cm tall. A brother, height 180 cm, died at age 18 years of ventricular septal defect and pulmonary hypertension. He looked like the surviving brother and quite different from other members of the family. Kaariainen (1982) concluded that the disorder is the same as that described by Simpson et al. (1975). Cleft of the lower lip was .....

A **keyword search** is valuable. Since the World Wide Web may contain some information on familial hormone deficiencies, a search of the OMIM database is indicated. To do this, one logs on to the OMIM home page by entering the URL–http://www.ncbi.nlm.nih.gov/omim. Then one clicks on "Search the OMIM Database" with the mouse and enters "gh and thyroid" as a search term. Note that "gh" is used as a search term rather than growth hormone because the latter is 2 words. Use of "gh" gives 36 hits, while "growth AND hormone" gives 271 hits. By using "gh AND thyroid," 7 disorders appear on the screen (Figure 2, below). The first entry (*173110 POU DOMAIN, CLASS 1, TRANSCRIPTION FACTOR 1; POU1F1)[4] is about the PIT1 transcription factor and includes an interesting paragraph:

> *Mutations of the* POU1F1 *gene in the human and Pit1 in the mouse are responsible for deficiencies of growth hormone, prolactin, and thyroid-stimulating hormone, while the production of ACTH, LH, and FSH are preserved. In contrast, patients with combined pituitary hormone deficiency due to homozygosity or compound heterozygosity for inactivating mutations of* PROP1 *(601538) cannot produce LH and FSH at a sufficient level and do not enter puberty spontaneously (Wu et al, 1998).*[5]

The case under consideration seems to fit the findings reported for *PROP1* mutations, so it is appropriate to review the article by Wu et al. On the Web, you can obtain a copy of the abstract by clicking the mouse on

Figure 2
OMIM Page Showing Results of Search Initiated Using "gh AND thyroid" as a Search String.

OMIM Home | Search

Select Entries from OMIM–
Online Mendelian Inheritance in Man
7 entries found, searching for "gh and thyroid"

---

*173110 POU DOMAIN, CLASS 1, TRANSCRIPTION FACTOR 1; POUIF1
#262500 PITUITARY DWARFISM II
*139320 GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA-STIMULATING ACTIVITY POLYPEPTIDE 1; GNAS1
#118450 ALAGILLE SYNDROME; AGS
*262600 PITUITARY DWARFISM III
*188545 THYROTROPIN-RELEASING HORMONE RECEPTOR; TRHR
*600239 G PROTEIN-COUPLED RECEPTOR 1; GPR1

SELECTED WEB SITES THAT CONTAIN INFORMATION ON GROWTH AND HORMONE DISORDERS

Summaries of Disorders for Professionals, Educators, and Laypeople

MEDLINE PubMed and Internet Grateful Med (http://www.nlm.nih.gov/databases/freemedl.html): Provides access to a cornucopia of scientific and medical publications in a searchable format.

Alliance of Genetic Support Groups, Inc. (http://www.geneticalliance.org): Genetic support groups voice the common concerns of children, adults, and families living with, and at risk for, genetic conditions.

American Diabetes Association (http://www.diabetes.org): For professionals and laypeople; http://www.childrenwithdiabetes.com is the online community for kids, families, and adults.

Chromosomal Variation in Man (http://www.wiley.com/products/subject/life/borgaonkar/access.html): A catalog of chromosomal variants and anomalies that includes citations on all common and rare chromosomal alterations, phenotypes, and abnormalities in humans. The database is organized by variations and anomalies, numerical anomalies, and chromosomal breakage syndromes.

Cytogenetic Resources (http://www.kumc.edu/gec/geneinfo.html): Database of normal and abnormal karyotypes, empiric risks for chromosome abnormalities, and maps of genes on chromosomes.

Endocrine Society (http://www.endo-society.org): Information on the Endocrine Society, fellow societies, organizations, and patient education groups as well as resources for scientists and physicians.

GeneMap'98 (http://www.ncbi.nlm.nih.gov/genemap98): Includes the locations of more than 30,000 genes and provides an early glimpse of some of the most important pieces of the human genome.

Genetic Conditions/Rare Conditions Support Groups & Information Page (http://www.kumc.edu/gec/support): For professionals, educators, and individuals seeking information on genetic disorders, birth defects, and chromosomal disorders.

Genetic Web Sites National Society of Genetic Counselors (http://www.kumc.edu/gec/geneinfo.html): Covers cancer, cytogenetics, genetics, hyperlipidemia, neurogenetics, single gene disorders, and support groups.

Helix (http://healthlinks.washington.edu/helix): Helix is a directory of laboratories providing testing for genetic disorders. Information on both research and diagnostic laboratories is included and labs are listed by disease name.

HGMD (http://www.uwcm.ac.uk/uwcm/mg/index.html): Links to locus-specific mutation databases available on the World Wide Web.

Human Growth Foundation (http://www.genetic.org/hgf): A lay organization established for parents and friends of children with various sorts of growth disturbances, including overgrowth, growth hormone deficiency, Turner syndrome, etc.

Idiogram Server (http://www.pathology.washington.edu/cytopages/idiogram_select.html): Includes figures of human chromosomes and translocations.

Information for Genetic Professionals (http://www.kumc.edu/gec/geneinfo.html): Covers genetic conditions; clinical genetics resources, clinical genetics centers, departments and clinics; genetics education centers; genetics courses, lectures, and educational materials; ethical, legal, and social implications of the Human Genome Project; and genetic computer resources.

International Society for Pediatric and Adolescent Diabetes (http://www.ispad.org): Presents news, membership rosters, and meeting dates.

Lawson Wilkins Pediatric Endocrine Society (http://lwpes.org): Features news, job listings, etc.

Magic Foundation (http://www.magicfoundation.org): A lay organization established for parents and friends of children with various sorts of growth disturbances, including overgrowth, growth hormone deficiency, Turner syndrome, etc.

March of Dimes (http://modimes.org): Information for professionals and families on birth defects.

National Association for Rare Disorders (NORD) (http://www.rarediseases.org): Rare disorder database includes information on symptoms, etiology, diagnostic tests, and treatment for families and professionals.

National Human Genome Research Institute (NHGRI) (http://www.nhgri.nih.gov): Contains information on the Human Genome Project and Ethical, Legal and Social Implications Policy.

Neurofibromatosis Home Page (http://nf.org): Contains information about neurofibromatosis and contacts for related resources.

NLM Site Map (http://www.nlm.nih.gov/sitemap.html): Includes MEDLINE, TOXNET, biotechnology information, cancer information, and links to DNA databases.

OMIM (http://www.ncbi.nlm.nih.gov/omim): Online Mendelian Inheritance in Man contains textual information, pictures, and reference information on genes and genetic disorders, including clinical findings, references, and gene maps. OMIM has many links to NCBI's Entrez database of MEDLINE articles and sequence information and many links to other databases.

Peds Endocrine Cedars Sinai Medical Center (http://www.csmc.edu/pediatrics/default.html): Available for sharing cases, asking questions, and disseminating information to pediatric endocrinologists.

Policy Statements From the American Academy of Pediatrics (http://www.aap.org): Contains policy statements and guidelines on the diagnosis and treatment of genetic disorders as well as newborn screening.

Policy Statements From the American College of Human Genetics (http://www.faseb.org/genetics/acmg/pol-menu.html): Contains a variety of policy statements about genetic diseases, genetic testing, and treatment of genetic disorders.

Primer on Molecular Genetics (http://www.ornl.gov/hgmis/publicat/primer/intro.html): A Department of Energy site that contains information on molecular genetics, genetic testing, and the Human Genome Project.

Quackwatch (http://www.quackwatch.com): Information on health fraud and quackery as well as alternative treatments such as nutritional supplements for Down syndrome.

Rare Genetic Diseases in Children (http://mcrcr2.med.nyu.edu): Intends to publicize, educate, and refer those interested in or concerned with the various lysosomal storage diseases.

Simulated Genetic Counseling Session (http://www.kumc.edu/gec/gcslm.html): Online simulated session that illustrates the process of genetic counseling.

Figure 3

NCBI/PubMed Page Showing Results of Search Initiated Using "gh AND thyroid AND gonadotropin AND familial" as a Search Term. Note That 7 Publications Match All 3 Items in the Search String and That the First 2 of These Contain Essential Information.

PubMed PubMed QUERY

Details | GH AND thyroid AND gonadotropin AND fami | Search | Clear

Docs Per Page: 20 ▼ Entrez Date limit: No Limit ▼

8 citations found

Display | Abstract report ▼ | for the articles selected (default all).

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❑ Rosenbloom AL, et al. [See Related Articles]
Clinical and biochemical phenotype of familial anterior hypopituitarism from mutation of the PROP1 gene.
J Clin Endocrinol Metab. 1999 Jan;84(1):50-7.
PMID: 9920061; UI: 99116789.

❑ Fofanova OV, et al. [See Related Articles]
Rarity of PIT1 involvement in children from Russia with combined pituitary hormone deficiency.
Am J Med Genet. 1998 Jun 5;77(5):360-5. Review.
PMID: 9632165; UI: 98293954.

❑ Wu W, et al. [See Related Articles]
Mutations in PROP1 cause familial combined pituitary hormone deficiency.
Nat Genet. 1998 Feb;18(2):147-9.
PMID: 9462743; UI: 98122575.

❑ Irie Y, et al. [See Related Articles]
Screening for PIT1 abnormality by PCR direct sequencing method.
Thyroid. 1995 Jun:5(3):207-11.
PMID: 8144848;UI:94193994.

❑ Watanabe S, et al. [See Related Articles]
Risk factors for leukemia occurrence among growth hormone users.
Jpn J Cancer Res. 1989 Sep;80(9):822-5.
PMID: 2513298;UI: 90094016.

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either of the following: (1) the Wu et al, 1998 hypertext at the end of the paragraph cited above; or (2) the Wu et al, 1998 hypertext in either the PIT1 (173110) or PROP1 (601538) entries, and then click on the PubMed ID (9462743) that follows the reference that appears. You then will see the abstract of the reference on your screen and you can print it. Since this is a PubMed document, you also can save it as a file on your computer, as shown at the bottom of the page, or you can order a complete copy through Loansome Doc™ as shown at the top. Alternatively, you can obtain copies of articles by clicking on MEDLINE under "Database Links" that are just below the TABLE OF CONTENTS of each entry (Figure 1, page 20). If you do a PubMed search for "gh AND thyroid AND gonadotropin AND familial," you will immediately find 8 related articles, the first 3 of which contain information that you may find helpful in the further evaluation and treatment of your new patient (Figure 3). As in the first case, you can carry out a HELIX search to find a lab that can conduct a molecular analysis of the *PROP1* gene.

Now there is a working diagnosis (*PROP1* defects), information on the pathogenesis, mode of inheritance, and the findings associated with the disorder, and a way to find a lab that helps confirm the working diagnosis. Obviously, after this you feel better prepared to talk with your patient's parents and to answer their questions.

CONCLUSIONS

The World Wide Web is here to stay. It offers an expedient way to find the answers to complex diagnoses and problems that previously had not been possible. It behooves every physician to capitalize upon the aids that the World Wide Web and computer technology provide. As is true for most things in life, some effort has to be put forth to develop the expertise needed to master the Web. Hopefully, this introduction will help you succeed.

ADDENDUM: Since this article was solicited and received, an article by Dr. Phillips regarding On Use of the WEB to DIAGNOSE GENETIC AND ENDOCRINE CASES has been placed on the Web. You can find it at the URL-http://bret.mc.vanderbilt.edu/genetics/html/ frame_education.htm.

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Effect of Growth Hormone Treatment on Adult Height of Children With Idiopathic Short Stature

Of 121 children with idiopathic short stature (ISS) entering the study to receive GH, 80 have reached adult heights after 3.5 to 10 years of GH therapy. The children were randomly assigned to either an observational control group or to treatment (0.1 mg/kg/3x weekly). The change in adult height relative to initial predicted height achieved with GH was compared with 2 groups of normal children, including 291 children with initial height SDS >-1 and bone age (BA) ≤10 years and 37 with height SDS <-1. In addition, the change in height of the 80 was compared with the change in height in untreated ISS patients (initial height SDS <-2).

The baseline and final characteristics of the 80 are recorded in Table 1, and the height SDS ± SEM (for chronologic age [CA]) versus treatment years are recorded in Figure 1. The mean baseline height SDS for the 121 ISS children was -2.7. The mean height SDS for age in the 69 treated for 5 years increased to -1.4. The 29 children treated for 7 years reached a mean height SDS of -1.0. Mean adult height also increased in the 80 compared with their initial predicted height. Sixty-five of the 80 (81%) had an increase. The mean (± SD) changes in heights from predicted heights of the treated boys and girls were 5.0 ± 5.1 cm and 5.9 ± 5.2 cm, respectively. Neither the control group of boys from the Fels Longitudinal Growth Study with basal height SDS of <-1 nor the control group of untreated ISS boys with basal height SDS <-2 reached their mean initial predicted height (mean change in height of -1.7 ± 4.2 cm and -4.2 ± 7.7 cm, respectively). Thirty-eight of 48 boys (79%) treated with GH exceeded their initial predicted adult height compared with only 2 of 11 (18%) of the untreated ISS boys. In addition, 24 of the 48 boys (50%) had a clinically important (>5 cm) increase in adult height as compared with only 1 of the 11 untreated boys. These results are summarized in Table 2 on page 24, as are the similar studies for girls.

Table 1
Baseline and Final Characteristics In 80 Children With Idiopathic Short Stature Treated With Growth Hormone Until Final Height*

	Boys (n=57)	Girls (n=23)
Baseline chronologic age	10.4 ± 1.8	9.7 ± 2.1
Baseline bone age	8.7 ± 1.6	8.2 ± 1.9
Baseline height SDS	-2.8 ± -0.5	-2.7 ± 0.4
Duration of growth hormone therapy (yrs)	6.0 ± 1.7	5.5 ± 1.7
Final height (cm)	165.5 ± 7.2	153.1 ± 4.8
Pretreatment predicted adult height (cm)	160.6 ± 6.4	147.2 ± 5.1
Final height minus pretreatment PAH (cm)	5.0 ± 5.1	5.9 ± 5.2
Midparental target height (cm)	170.7 ± 4.5 (n=54)	159.0 ± 3.4
Chronologic age at final height (yrs)	18.1 ± 1.6	17.2 ± 2.0

*Values are given as means ± SD.

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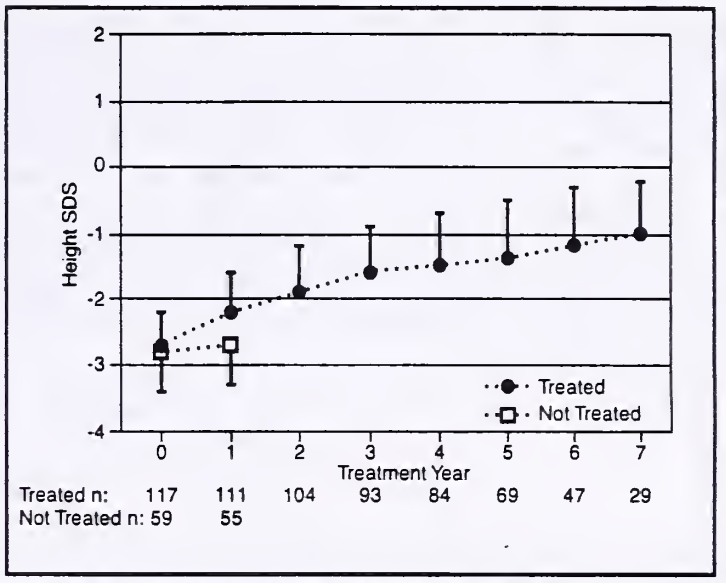
Figure 1
ISS Treated With GH: Height SDS ± SEM for Chronologic Age Versus Treatment Year for Treated and Untreated Controls



Reprinted with permission from Hintz RL, et al. *N Engl J Med* 1999;340:502-507.

Since approximately one half of ISS children treated with GH had a >5-cm increase in adult height, as compared with initial predicted height, an important question must be addressed: Is prediction of the end result possible? In this respect, no relationship was found between the increase in adult height and the CA, BA, height age, predicted adult height, peak GH response, 12- or 24-hour integrated GH levels, or any of the insulin-like growth factor-related peptides at initiation of therapy. There also was no correlation of ultimate gain with the growth response in the first 12 or 24 months of GH treatment or the total length of treatment.

After a cogent discussion of the variability of responses and the ethics of treating ISS children, the authors concluded:

> *If there were no long-term benefit of treatment with GH in ISS, there would be no reason to treat and thus no ethical problem. However, our study demonstrates that there is a significant potential benefit of GH treatment. Thus the decision to treat must involve a difficult judgment of relative benefits, risks, and the cost of treatment.*

Hintz RL, et al. *N Engl J Med* 1999;340:502-507.

Editor's comment: *Much has been written in the literature regarding the possible treatment of ISS with GH. Many articles, both pro and con, regarding this have been abstracted in* GROWTH, Genetics, & Hormones *(Vol 11[4]:8; Vol 12[1]:14; Vol 15[1]:7-8). The study by Hintz et al abstracted here is as close to a definitive study that has been done. Each interested reader of this abstract should review the entire article in the* New England Journal of Medicine *and possibly others before deciding whether in his/her opinion GH treatment is justifiable. As for myself, I judge each instance on the characteristics and merits of the case and cost.*

Fortunately, the creation of the Genentech Foundation for Growth and Development has made it possible for several psychological studies to be initiated. These will be reported subsequently regarding the psychological importance of a possible modest gain in height among such patients as reported here. Unfortunately, these studies will not be reported for another 2 to 3 years.

Robert M. Blizzard, MD

2nd Editor's comment: *This interesting report provides very good data regarding the use of GH for the treatment of children with ISS. Although these children showed an increase in final adult height, they did not exhibit a major improvement even after 10 years of GH therapy. The advantage of 2 or 3 inches gain in final height has to be correlated with the cost and the long-term duration of treatment needed to achieve such a modest gain. However, we now have clear data to present and to discuss with those patients and their families when evaluating the need for GH treatment.*

Fima Lifshitz, MD

Table 2
Change in Final Height in ISS Treated With GH Compared With the Change in 2 Untreated Control Groups (cm)

	Boys	Girls
	Mean (95% CI)	
△Ht: ISS treated with GH (48 boys, 21 girls)	5.0 (3.6 to 6.3)	5.9 (3.7 to 8.1)
△Ht: ISS treated with GH minus △Ht: controls (Ht SDS <-1)	6.7 (3.7 to 9.6)	2.3 (-0.6 to 5.1)
△Ht: ISS treated with GH minus △Ht: controls (Ht SDS <-2)	9.2 (5.5 to 12.8)	5.7 (2.1 to 9.4)

Ht = height
△Ht = final height minus initial predicted adult height

Reprinted with permission from Hintz RL, et al. *N Engl J Med* 1999;340:502-507.

A Study of Females With Deletions of the Short Arm of the X Chromosome

A clinical and molecular study of 25 females with deletions of the short arm of the X chromosome was undertaken. The deletion breakpoints, the parental origin, and the activation status of the deleted X chromosomes were determined.

The short stature observed in Turner syndrome (TS) and in patients with terminal Xp deletions results from the deletion of a homeobox gene, *SHOX*, which escapes X-inactivation and is located in the pseudoautosomal region of Xp. In determining parental origin of the X chromosome with deletions, the paternal X chromosome was defective in the vast majority. Parental disomy of the X chromosomes was excluded in 24 of the 25 deleted X chromosomes.

In all cases where the breakpoint was in or proximal to Xp22.1, the deleted X was late replicating in all cells observed.

Of the 25 patients, 23 had short stature resulting from the deletion of the *SHOX* gene in the pseudoautosomal region of Xp. None of the patients in this study had a webbed neck, which is lymphomatous in origin, although 49% of 45,X individuals in a recent review (Ogata and Matsuo. *Human Genetics* 1995;95:607-629) had neck webbing. The studies suggest that a gene (or genes) responsible may reside on Xq or very proximal on Xp. Six of 18 patients examined were found to have a low hairline posteriorly. The most distal breakpoint in such a patient was Xp22.31. Congenital edema of the extremities was described in 2 cases with breakpoints in Xp22.3 but not in any of the other cases, even when breakpoints occurred in the very proximal part of Xp. None of the patients with breakpoints distal to Xp11 had any cardiovascular problems; however, breakpoints in or proximal to Xp11 were sometimes associated with aortic valve abnormalities.

The authors concluded that the apparently normal ovarian function seen in 2 cases of females with a single copy of the *DFFRX* gene suggests that the ovarian failure seen in cases of 45,X TS may result from a mechanism other than haploinsufficiency of *DFFRX*. The absence of neck webbing in any of the patients studied suggests that the gene for this feature may lie on Xq or very proximal Xp. There were no consensus breakpoints for the other stigmata associated with lymphatic abnormalities, skeletal abnormalities, or cardiac and renal abnormalities. The presence of excess melanocytic nevi is associated with breakpoints proximal to Xp22. There is some evidence for the presence of a gene for some of the soft features of TS, located in Xp22.3, and subject to X-inactivation. In cases of distal terminal deletions, the deleted X may remain active in a proportion of cells, resulting in a Turner-like phenotype, dependent on the degree of mosaicism and the tissue specificity.

James RS, et al. *Hum Genet* 1998;102:507-516.

Editor's comment: *This presentation of a very detailed clinical and cytogenetic study contributes significantly to a better understanding of the locations of the genes on the X chromosome. We have come a long way since Ferguson-Smith determined in 1965 that deletions of the whole short arm of the X chromosome in females are associated with short stature, gonadal dysgenesis, and the classic stigmata of TS. However, 34 years have passed since then. With our ever-advancing technology, probably we will know the complete genome in the next decade. We then will understand many more intricacies of gene interaction, and the time interval to learn all this will be short.*

Robert M. Blizzard, MD

Calcium Metabolism and Growth During Early Treatment of Children With X-Linked Hypophosphatemic Rickets

The authors administered calcitriol (20 to 40 ng/kg/d) in 2 divided doses and phosphate 40 to 60 mg/kg/d in 5 divided doses to 8 infants (1 male) with X-linked familial hypophosphatemic rickets (XLHR). This syndrome is a result of an inactivating mutation in *PEX*, a gene that encodes an endopeptidase whose substrate may be the elusive "preprophosphotonin." The subjects ranged in age from 3 to 12 weeks at diagnosis and initiation of therapy and were followed for 1 to 4 years.

Treatment led to a decline to normal or nearly normal serum concentrations of alkaline phosphatase and urinary excretion of hydroxyproline, but little rise in serum phosphate concentrations. Secondary hyperparathyroidism developed occasionally, usually when phosphate intake exceeded 50 mg/kg/d. Nephrocalcinosis (grades 1 and 2) appeared in 3/8 infants without compromise of renal function. The infants grew reasonably well, with lengths maintained within the normal ranges in 6/8 patients at the conclusion of the study (see Figure). Genu varum developed in 3 children while genu valgum developed in 1. The authors conclude that early treatment with calcitriol at a daily dose of at least 30 to 40 ng/kg and phosphate at a maximal daily dose of 40 to 50 mg/kg improves mineral metabolism and seems to minimize severe growth delay and leg deformities.

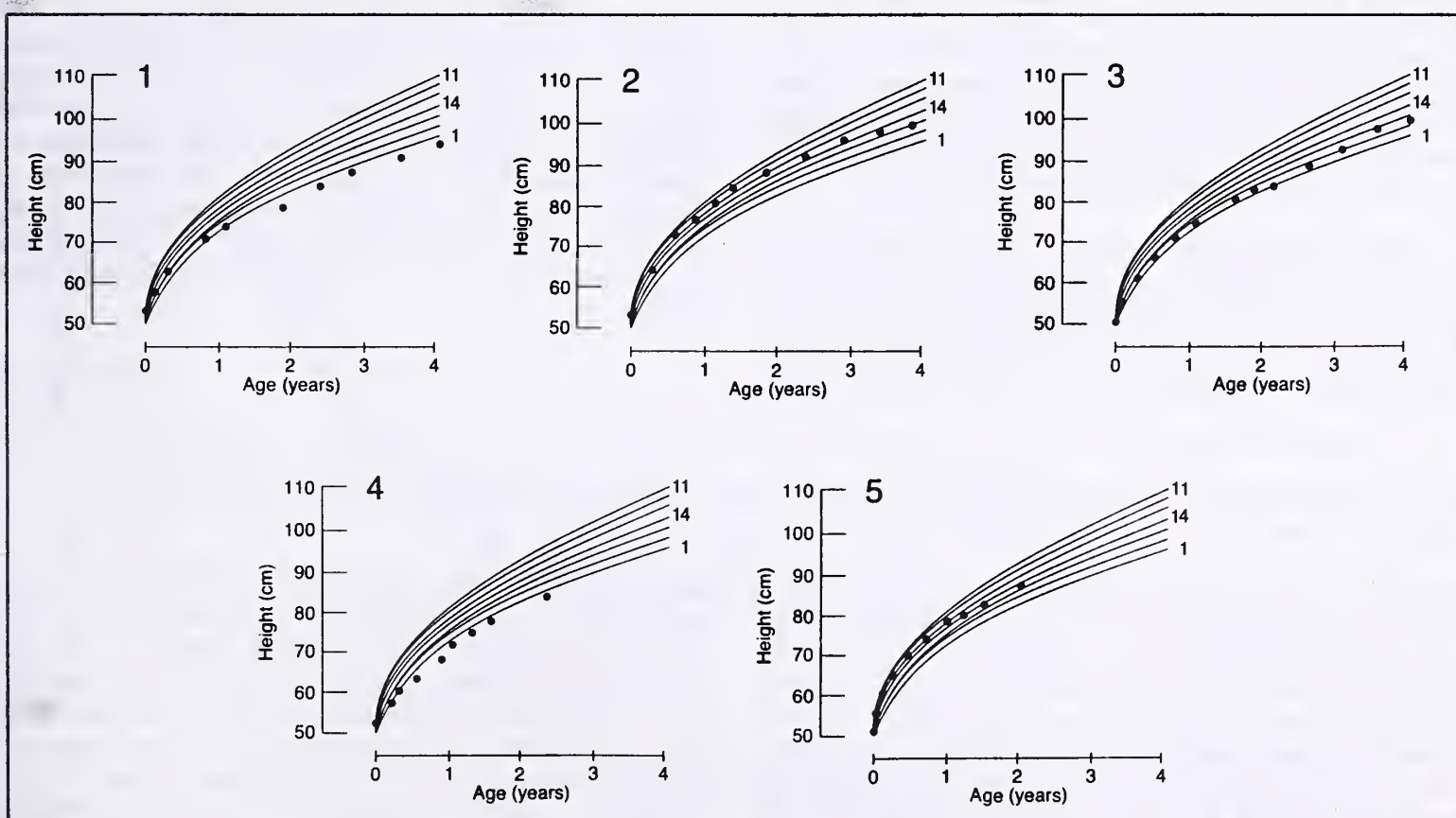
Editor's comment: *Most children with XLHR have significant retardation of linear growth and deformities of the lower extremities despite administration of appropriate therapy with calcitriol and phosphate. In many instances this is the result of noncompliance with the arduous therapeutic regimen of multiple daily doses of phosphate. Treatment is not only difficult but also hazardous, with distressingly frequent periods of hypercalciuria (leading to nephrocalcinosis), hypercalcemia, and secondary hyperparathyroidism that necessitate frequent chemical and radiographic monitoring.*

Several investigators have reported the beneficial effects of rhGH on the growth of children with XLHR. The experience of this writer with rhGH also has been encouraging and has seemingly made the management of calcitriol and phosphate dosing less difficult. The identification of "phosphotonin" is awaited as it may offer a more specific therapeutic (and hopefully less toxic) agent for this illness than is now available.

Allen W. Root, MD

Kruse K, et al. *Eur J Pediatr* 1998;157:894-900.

Figure
Growth Charts of 5 Study Patients With XLHR Treated the Longest With Phosphate and Calcitriol



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Efficacy and Safety of Lovastatin in Adolescent Males With Heterozygous Familial Hypercholesterolemia: A Randomized Controlled Trial

Stein et al report the experience of 132 patients recruited from 14 different centers to participate in a study evaluating the safety and efficacy of lovastatin treatment in children with heterozygous familial hypercholesterolemia (HeFH). Adolescent boys aged 10 to 17 years who had followed the American Heart Association (AHA) pediatric diet for at least 4 months were recruited in this randomized, placebo-controlled study. The inclusion criteria for HeFH were: (1) low-density lipoprotein cholesterol (LDL-C) values of at least 4.9 mmol/L (189 mg/dL) and no more than 13.0 mmol/L (503 mg/dL) and at least 1 parent had an LDL-C value of at least 4.9 mmol/L (189 mg/dL); or (2) LDL-C values of at least 5.7 mmol/L (220 mg/dL) and no more than 13.0 mmol/L (503 mg/dL) and a parent who had died of coronary artery disease (CAD) with no available lipid values. These LDL-C entry criteria had to be met prebaseline. Both groups in the study were similar as to age, height, weight, smoking rate, blood pressure, testicular volume, and baseline serum lipid profile.

Prior to randomization, all eligible participants received placebo during the last 4 weeks of an 8-week stabilization period in addition to the AHA diet. After randomization, they were administered either placebo or lovastatin immediately prior to the evening meal during the following 24 weeks (period 1). Lovastatin was started at 10 mg/d and increased at 8 and 16 weeks to 20 and 40 mg/d, respectively. During the second 24-week period (period 2), lovastatin was given at 40 mg/d. Those who received placebo during period 1 continued receiving placebo during period 2. Subjects were followed every 4 weeks during period 1 and every 6 weeks during period 2. Clinical assessment, including growth assessment and serum cholesterol, triglyceride, LDL-C, high-density lipoprotein cholesterol, apolipoprotein B (Apo B), transaminases, and creatine kinase levels, were determined at every visit. Total protein, albumin, ferritin, glucose, and vitamins A, D, and E serum levels also were determined to evaluate nutritional status.

There was a positive family history for familial hypercholesterolemia in 74% of the 132 randomized subjects. In 56% the mother was affected while in 44% the father was affected. The mean age of onset of CAD of the affected parents was 37 years. Lovastatin had no significant effect on growth parameters throughout the study. Sexual maturation progressed similarly in both groups. Baseline total cholesterol, LDL-C, and Apo B serum concentrations were elevated, as expected in individuals with HeFH. Lovastatin reduced total cholesterol and LDL-C levels at all dosages and Apo B at 40 mg/dL during period 1 (Apo B was not measured during treatment with lower dosages). Continued therapy with lovastatin reduced LDL-C and Apo B levels 25% and 22%, respectively, during period 2. Although a gradual upward trend from baseline levels in alanine aminotransferase was noted, no significant differences were found between groups at week 48. Biochemical measurements to assess nutritional status did not show differences at baseline or after 48 weeks of lovastatin treatment except for a reduced tocopherol level.

The authors concluded that lovastatin did not affect growth and effectively reduced serum LDL-C and total cholesterol levels.

Stein EA, et al. *JAMA* 1999:281(2):137-144.

Editor's comment: *Familial hypercholesterolemia is a worrisome genetic condition that requires aggressive lipid-lowering therapy. Failure to control hypercholesterolemia has been associated with high mortality and frequent life-threatening cardiovascular episodes, often seen early in life. Thus, this interesting report demonstrates the importance of these therapeutic interventions in the pediatric population. The study itself demonstrates modest reductions (21%) in serum lipid level after 48 weeks of intense therapy. This reduction occurred with the help of a low-fat, low-cholesterol diet without alterations in growth and development while other nutritional indexes remained intact. This is important since dietary restrictions to lower serum cholesterol may result in a decreased growth rate. This paper also remarks on the significance of the potential prevention of the high morbidity associated with increased serum cholesterol levels. However, long-term studies are necessary to corroborate the safety and effectiveness of lipid-lowering therapies for prolonged periods beginning in childhood.*

Fima Lifshitz, MD

Weight Control and Risk Factor Reduction in Obese Subjects Treated for Two Years With Orlistat: A Randomized Controlled Trial

A randomized, double-blind, placebo-controlled study using orlistat, a gastrointestinal lipase inhibitor, to promote weight loss is reported by Davidson et al. A total of 1,187 obese subjects older than 18 years with a body mass index of 30 to 43 kg/m^2 and absence of weight loss in the previous 3 months were recruited from 18 different research centers in the United States. Qualified subjects received a controlled-energy diet that provided 30% of energy intake as fat during a 4-week lead-in period. Individual energy intake was calculated according to the estimated daily maintenance energy requirement (1.3 x calculated basal metabolic rate) minus 2,100 to 3,360 kj/d. After the 4-week lead-in period, 892 subjects, who had a treatment compliance rate of ≥75%, were randomly assigned to receive placebo (25% of the subjects, n=224) or orlistat 120 mg (75% of the subjects, n=668) for 52 weeks. Subjects who received placebo in the first year who had a ≥70% compliance rate received placebo for an additional 52 weeks. Orlistat-treated subjects who completed 1 year with a compliance rate of >70% received placebo, orlistat 120 mg, or orlistat 60 mg for an additional 52 weeks. Medical history, body weight determination, clinical chemistry, thyroid function, fasting lipid levels, fasting glucose and insulin, and 3-hour glucose tolerance tests were performed at the time of randomization and at the end of years 1 and 2.

A weight loss of approximately 2.3% of the initial body weight was noted during the 4-week placebo lead-in period. Mean age, weight, and body mass index were similar in both groups after randomization. Individuals who received orlistat had significantly greater weight loss (8.8% ± 0.4%) compared with controls (see Figure). Subjects treated with orlistat 120 mg during year 1 and who received orlistat 120 mg during year 2 regained significantly less of their first-year weight loss (35.2% regain) compared with those who received orlistat 60 mg (51.3% regain) or placebo (63.4% regain). Systolic and diastolic pressure significantly decreased with orlistat 120 mg versus placebo. Decrease in mean waist circumference was greater in the orlistat-treated group compared with the placebo group after 2 years of therapy. Serum cholesterol and low-density lipoprotein cholesterol (LDL-C) levels decreased 8% during the 4-week placebo lead-in period. Serum cholesterol and LDL-C levels declined in the orlistat-treated group during year 1. Fasting serum glucose levels increased less and fasting serum insulin levels decreased in the orlistat-treated group over 2 years versus placebo. There were more undesirable gastrointestinal events (ie, flatus, oily spotting, fecal urgency, oily evacuation, fecal incontinence, and increased defecation) associated with orlistat treatment.

The authors concluded that orlistat promoted weight loss, lesser weight regain, and improved fasting cholesterol, LDL-C, and insulin levels.

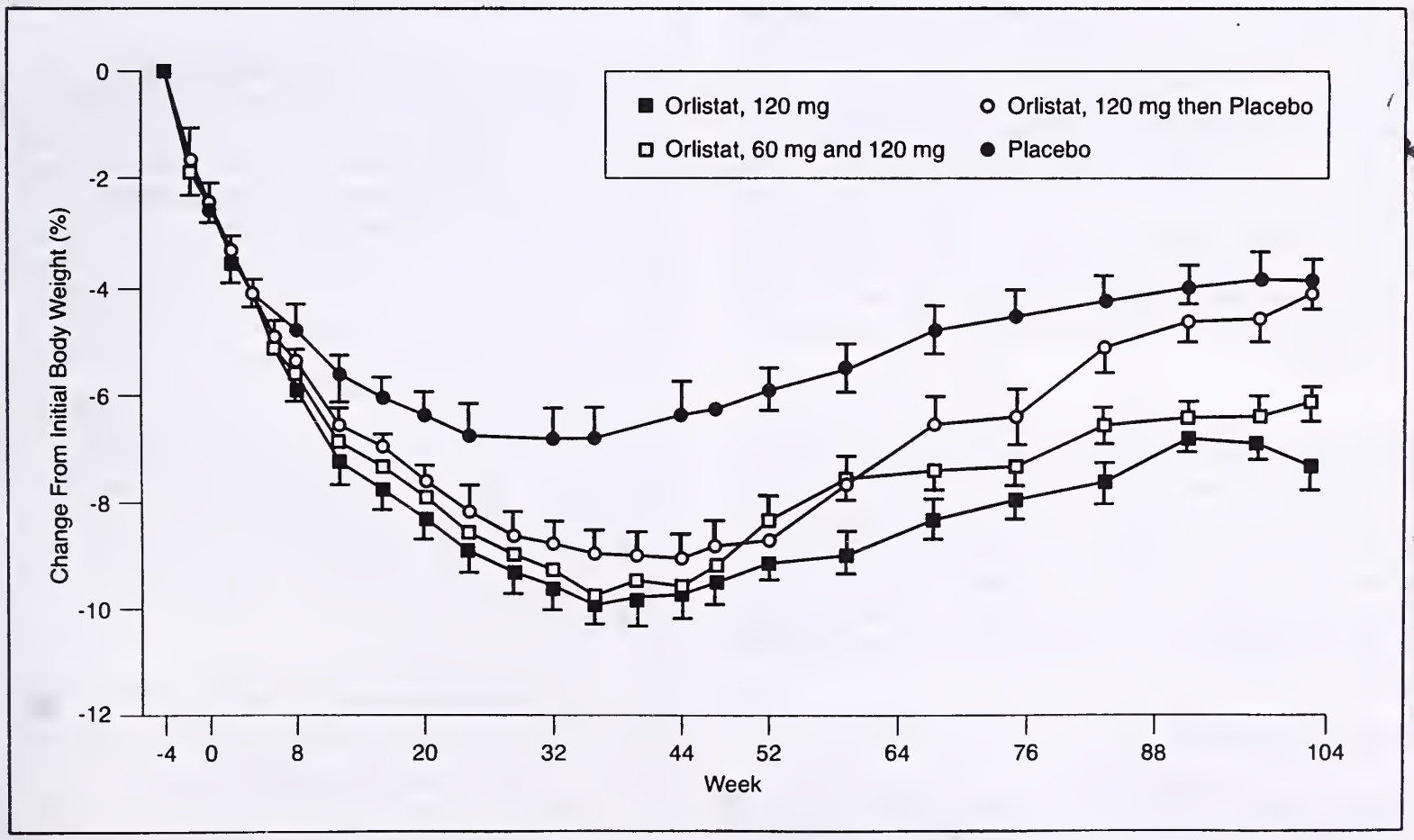
Davidson MD, et al. *JAMA* 1999:281(3):235-242.

Editor's comment: *Obesity has reached epidemic proportions, especially in developed countries. Obesity and its metabolic abnormalities are associated with very high morbidity and mortality. This interesting study supports the European data reported by Sjostrom et al (*Lancet *1998;352:167-173) in which orlistat promoted weight loss, reduced weight regain, and lowered serum lipids and insulin levels over a 2-year period. Orlistat, a gastrointestinal lipase inhibitor, exerts its action by producing fat malabsorption without being absorbed or metabolized. Thus, it would not have the potentially life-threatening side effects (ie, valvular heart disease and primary pulmonary hypertension) described for fenfluramine-phentermine (*N Engl J Med *1997;337:581-588).*

Even though much literature has been published regarding pharmacotherapy for obesity in adults, reports concerning pediatric experience are limited. Therefore, it will be interesting and important to have more information on the use of orlistat in treating severe obesity in the pediatric population, where obesity usually begins. Both pharmaceutical firms and the FDA are urged to support such studies.

Fima Lifshitz, MD

Figure
Mean Body Weight Change (± SEM) During 2 Years of Double-Blind Treatment



Reprinted with permission from Davidson MH, et al. *JAMA* 1999;281:235-242.

A Gene Encoding a Transmembrane Protein Is Mutated in Patients With Diabetes Mellitus and Optic Atrophy (Wolfram Syndrome)

Wolfram syndrome is an autosomal recessive neurodegenerative disorder defined by young-onset, nonimmune insulin-dependent diabetes mellitus (IDDM), progressive optic atrophy, and diabetes insipidus. It is also called the DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) syndrome. Most patients with this progressive disorder eventually develop all four cardinal manifestations and die prematurely with widespread atrophic changes throughout the brain. Onset of IDDM occurs at a mean age of 6 to 8 years. The pancreatic islets are atrophic and insulin-producing beta-cells are selectively absent. The disease is believed to account for 1 of every 150 patients with young-onset IDDM.

The investigators confirmed the localization of the gene to chromosome 4p and isolated a gene (*WFS1*) from this region with 8 exons encoding a probable cell membrane protein with 890 amino acids that is related to the prenyltransferase a α-subunit. Hydrophilic amino and carboxyl terminal regions encompass a central hydrophobic core. Further analysis suggested that the protein had approximately 10 transmembrane domains. The function of *WFS1* protein was not identified but its mRNA was expressed in pancreatic islets, brain, heart, skeletal muscle, kidney, and placenta. Inactivating homozygous and compound heterozygous mutations in exon 8 of *WFS1* were found in all affected members of 6 families, but not in control subjects, including deletions, insertions, and nonsense and missense mutations. The authors conclude that mutations in *WSF1* are related to Wolfram syndrome and suggest that the WSF1 protein is important in the maintenance of islet cell and brain function.

Inoue H, et al. *Nature Genet* 1998;20:143-148.

Editor's comment: *Further proof of the relationship of WFS1 to Wolfram syndrome awaits the characterization of the phenotype in a mouse model in which the homologous gene has been "knocked out." Identification of the biologic function of WFS1 protein will be of great interest as in its absence pancreatic islets and beta cells, as well as the brain, atrophy. Thus, the WFS1 protein may be involved in the regulation of organ-specific apoptosis. Perhaps it is even an "antiaging" agent!*

Allen W. Root, MD

Bone Age in 116 Untreated Patients With Turner's Syndrome Rated by a Computer-Assisted Method (CASAS)

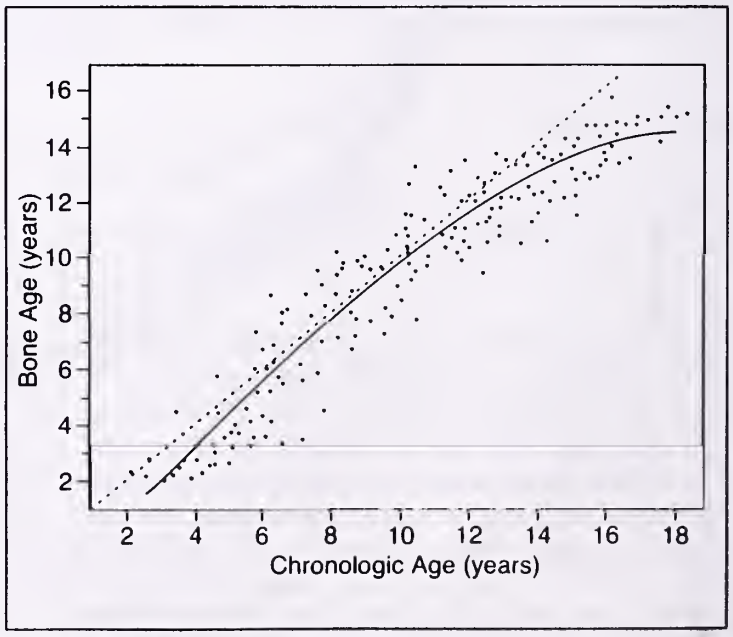
The investigators employed the computer-assisted skeletal age system (CASAS) to examine skeletal maturation in 265 radiographs of 116 untreated patients with Turner syndrome (TS). CASAS is based on the TW2-RUS (Tanner-Whitehouse 2–Radius, Ulna, Short Bones) method of bone age (BA) determination. In this procedure, the operator identifies on the radiograph the bones of the wrist and hand to be scored; the computer program then digitizes and analyzes the images and computes a score that is translated into a BA. There is apparently good reliability between the CASAS BA and that interpreted by human operators (Tanner JM, et al. *Hormone Research* 1994; 42:487).

In this study, the investigators reported that in untreated TS subjects the BA was delayed relative to chronologic age (CA) from the 3rd to the 6th years of life, advanced rapidly between 6 and 7 years of age, was similar to CA between 7 and 12 years of age, and was delayed after 12 years of age; epiphyseal fusion was not achieved until after 17 years of age (see Figure). The authors provided normative data for BA in TS and compared their data with those reported using the Greulich and Pyle and TW2-RUS atlases.

The authors concluded:

> *In this study a reference curve was presented for bone age progression in TS for use in clinical practice. Knowledge of bone age and consequently accurate bone age rating at diagnosis and during longitudinal follow-up is essential in order to be able to counsel the patient, advise on therapy,*

Figure
Plot of Bone Age Ratings Versus Chronologic Age of 116 Untreated Patients With Turners Syndrome: A Regression Curve to the Data Was Fitted by Polynominal Regression Analysis.



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initiate treatment and monitor development during treatment. The determination of bone age using a computer-assisted system proved a valid and reliable method. This will compensate for the additional time that needs to be invested. Future studies evaluating the effect of growth-promoting treatment in TS, by growth hormone or other means, should use such a computerized method for the determination of bone age.

Schwarze CP, et al. *Acta Paediatr* 1998;87:1146-1150.

Editor's comment: *There are currently 2 computer programs for the analysis of BA, both based on the TW2-RUS system: (1) CASAS, and (2) the Royal Orthopedic Hospital Skeletal Aging System – in which the digitized image can be obtained from a radiograph or directly from files and the bones are recognized by their position on the image (Aicardi G, et al.* Acta Med Auxol *1998;30:121-127). In addition, investigators at the Universities of Genoa and Florence are in the preliminary stages of developing computer programs for BA determination. Apparently, computer programs utilizing the Greulich and Pyle atlas or other methods for BA determination have yet to be developed. One wonders if current technology permits the computerized construction of 3-dimensional images of the wrist, hands, and other epiphyses that might afford further insight into the developmental changes that accompany growth and development of the skeleton and perhaps even better assessment of skeletal maturation–perhaps by determination of bone volume or other measurement. Regardless, more widespread utilization of CASAS is important for consistency within and among institutions.*

Allen W. Root,

Difference in Height Associated With a Translation Start Site Polymorphism in the Vitamin D Receptor Gene

Because calcitriol (1,25-dihydroxyvitamin D_3) is an important regulatory factor in the differentiation and proliferation of chondrocytes, the investigators speculated that various isoforms of the vitamin D receptor (VDR) might influence the effect of calcitriol on these processes and ultimately on linear growth. The VDR is polymorphic, in part because of 2 possible "start sites" in exon 2, one encoding a 427 amino acid peptide, the other a 424 amino acid molecule. The 2 isoforms are designated T and C, respectively, for the polymorphic alleles ATG/ACG at the first start site.

The authors examined the relationship between the presence/absence of the 2 variants of the VDR and the adult height in 90 healthy Japanese females (Figure), the height at age 13 years of 159 healthy Japanese children, and the height of 24 children aged 6 to 10 years with constitutional short stature (<1.5 SD), mostly with parents of normal height. They found that adult females with the CT genotype (ie, heterozygotic subjects with both the long and short forms of the VDR) were 4.4 cm taller than those with the CC genotype (ie, homozygous for the short form of the VDR) and 2.7 cm taller than those with the TT genotype (ie, homozygous for the long form of the VDR). There was no relationship between VDR genotype and age at menarche or between height and age at menarche in this population. Among the children (87 female, 72 male), height SDS also was greatest in those with the CT genotype. The frequency of the 3 VDR genotypes was CT 0.51, CC 0.37, and TT 0.12 in 249 normal subjects. Among constitutionally short children, the distribution of genotypes was CT 0.21, CC 0.62, and TT 0.17. Thus, the frequency of the CT genotype was lower in children with constitutional short stature than in the general population.

The investigators suggest that the VDR genotype very possibly influences the growth of children and the height of adult females in the population studied, although the mechanism by which this effect might act is unknown, as are the complementary roles played by the polymorphic variants of the VDR.

Minamitani K, et al. *Pediatr Res* 1998;44:628-632.

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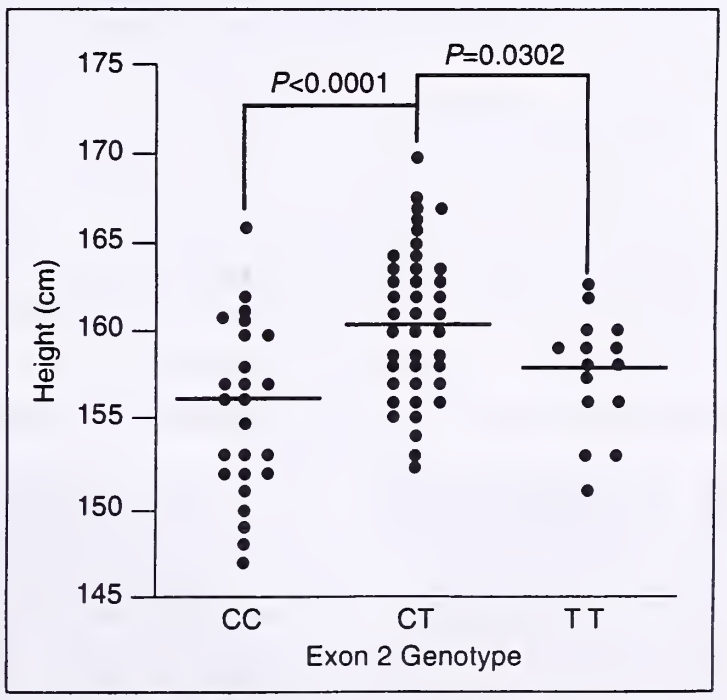
Figure
Exon 2 Polymorphism and Adult Height in 90 Female Subjects



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Editor's comment: *It would have been interesting to learn if the sex of the subject influenced the height-promoting effect of the polymorphic forms of the VDR, but no data were provided on the relationship of the VDR genotype to the adult height of Japanese men or to the group of children studied. In addition to the exon 2 polymorphism of the VDR, there are several other polymorphic variants of the VDR. Suarez et al reported that absence of the BsmI endonuclease site in intron 8 (homozygous for the presence of the endonuclease site designated BB) was associated with greater length and weight in females at 2 years of age than those with the genotype bb (homozygous for the presence of the endonuclease site), while the size of those with genotype Bb (heterozygous for the presence of the endonuclease site) was intermediate. On the other hand, 2-year-old BB males were smaller than those with either the Bb or bb genotype. Subsequently, these investigators observed that there was an interactive effect upon growth in male infants between the polymorphic genotypes of the estrogen receptor and the VDR, although the mechanism remains enigmatic. The polygenic mechanisms that affect growth and stature are slowly being deciphered. In addition to the effects of* SHOX *and* LHß *on growth, we may now add the* VDR *and the* ER *genes.*

Allen W. Root, MD

Suarez F, et al. *J Clin Endocrinol Metab* 1997;82:2966-2970.
Suarez F, et al. *J Clin Endocrinol Metab* 1998;83:3563-3568.

Role of Nonexercise Activity Thermogenesis in Resistance to Fat Gain in Humans

The authors studied the mechanisms by which some individuals are able to prevent substantial weight gain when ingesting excessive calories while others cannot so do. For 8 weeks, 16 healthy, nonobese young adults (12 males, 4 females) were fed a diet that had 1,000 calories in excess of that necessary for weight maintenance. Body composition was measured by dual energy X-ray absorptiometry. Total energy expenditure (TEE) was determined by quantitating carbon dioxide production. TEE is composed of basal metabolic rate (BMR), postprandial thermogenesis (PPT), and physical activity thermogenesis. BMR was assessed by indirect calorimetry to measure oxygen consumption and carbon dioxide production. PPT also was measured by indirect calorimetry. Thermogenesis due to total physical activity was calculated as TEE minus the sum of BMR and PPT. The latter was subdivided into volitional exercise, which was maintained at low and constant levels and assessed by pedometer, and nonexercise activity thermogenesis (termed NEAT), which was calculated as the difference between total physical activity and volitional physical activity. They found: (1) individual fat gain varied 10-fold (0.36 to 4.23 kg); (2) fat gain was inversely related to TEE; (3) on average, 43% of the excess calories were stored, and 53% were expended; (4) a 5% increase in BMR accounted for 8% of the excess energy ingested; (5) a 14% increase in PPT; (6) NEAT increased on average by 66% during overfeeding, but there were wide interindividual differences in NEAT (-98.3 to +692 kcal/d); and (7) NEAT was inversely related to the gain in fat mass. The investigators concluded that "activation of NEAT" explained individual variability in weight/fat increase during overfeeding.

Levine JA, et al. *Science* 1999;283:212-214.

Editor's comment: *These investigators have NEATly documented what we have been taught for many decades–that obese subjects expend far fewer calories than nonobese subjects in everyday activities of living such as sitting, standing, and "existing." Obese individuals sit and stand in an impassive, almost motionless manner that conserves every possible calorie. They choose to sit rather than stand whenever possible. Now, the question is, How does one "activate" NEAT, that is, can we induce fidgeting? Since NEAT appears to be a familial trait, it is likely to be of multifactorial/genetic origin. Among the factors that may influence NEAT might be stimulation of the sympathetic nervous system, leading to uncoupling of oxidative phosphorylation in brown fat and synthesis of or response to leptin or other appetite and energy expenditure regulating agents. Interestingly, Levine and colleagues found that the 4 female volunteers had the lowest increases in NEAT. The significance of this gender-related difference awaits further evaluation. The accompanying commentary (Ravussin E, Danforth E Jr.* Science *1999;283:184-185) also is recommended reading.*

Allen W. Root, MD

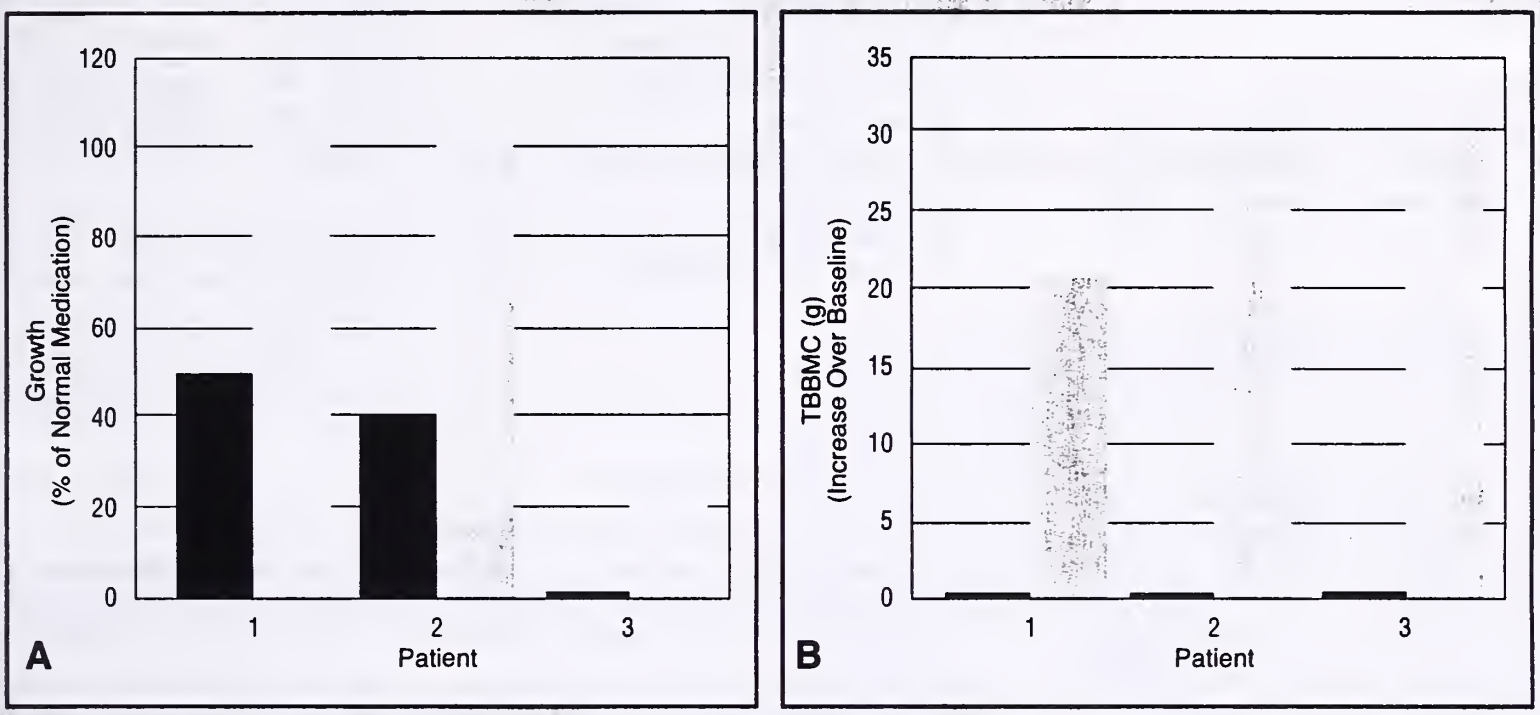
Cellular Therapy May Be Successful for Severe Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a relatively common autosomal dominant disorder of connective tissues. It results from mutations of genes encoding the $\alpha 1$ or $\alpha 2$ chain of type I collagen that lead to varying degrees of generalized osteopenia with fractures, progressive deformities, and growth deficiency. Until the recent introduction of the bisphosphonate compound, pamidronate, which shows promise as an agent for increasing bone density, there has been no therapy for OI other than symptomatic treatment. However, Horwitz et al now report encouraging results from the transplantation of bone marrow-derived mesenchymal stem cells in 3 children with severe OI.

The children ranged in age from 13 to 32 months. They had clinical phenotypes consistent with OI type III and documented mutations of *COL1A1* or *COL1A2*. After bone marrow ablative chemotherapy, each received a bone marrow infusion from an HLA-matched sibling (partial or complete). The children were evaluated extensively for at least 6 months.

Two of the children showed complete hematopoietic engraftment, while the third exhibited partial engraftment. Osteoblasts cultured from iliac bone of the first 2 children after transplantation showed 1.5% to 2 % donor cells. Comparison of pretrans-

Figure
(A) Growth rates of the patients during the 6 months immediately before (■) and after (□) transplantation. The values are percentages of the median growth of unaffected children of the same age and sex. (B) Increase of total body bone mineral content (TBBMC) at approximately 100 days after transplantation (□). Dual energy X-ray absorptiometry scans, obtained just before transplantation, served as the baseline. The predicted increase of TBBMC (■), based on an increase (if any) in the child's weight, is shown for comparison.



Reprinted with permission from Horwitz EM, et al. *Nature Med* 1999;5:309-313.

plantation to posttransplantation bone histology revealed changes consistent with enhanced bone formation. Similarly, bone mineral content increased considerably in all 3 patients following transplantation. All 3 children showed substantial clinical improvement. Growth velocity, which had been below normal before transplant, increased dramatically, especially during the first 100 days (Figure). Fracture rates dropped in all 3 children.

The authors concluded that marrow derived-osteoblastic precursor cells are capable of populating bone tissues of transplant recipients, where they attentuate the biochemical, structural, and clinical abnormalities associated with OI. They were unable to fully explain how such a small proportion of cells can produce such a substantial improvement in 3 parameters. Both the authors of this paper and of an accompanying editorial caution that questions remain regarding the long-term viability of this therapy.

Horwitz EM, et al. *Nature Med* 1999;5:309-313.
Gerson SL. *Nature Med* 1999;5:262-264.

Editor's comment: *OI has long been considered a good potential candidate for cellular therapy because of the accessibility and the dynamic nature of trabecular bone. In theory, donor cells that home to bone marrow have ready access to the trabecular surfaces on bone, and constant remodeling provides a means to capture donor cells within trabeculae. This report demonstrates that at least in the short term, osteoblastic precusors can be transferred by transplantation and that these theoretical considerations hold up clinically. Of course, more time and more patients will be needed to validate this therapeutic strategy. Nevertheless, the results are very promising.*

William A. Horton, MD

Instructions: The Post-Program Self-Assessment/Course Evaluation Answer Sheet can be found on the center page of the issue. Please follow the instructions listed there to receive CME Category 1 credit.

1. Access to information on the signs and symptoms of rare or recently discovered disorders can be located by surfing the Web.
   a) True
   b) False

2. OMIM is an acronym for:
   a. Online Mendelian Inheritance in Man
   b. Online Medical Information for Man
   c. Ontime Mendelian Inheritance in Man
   d. Ontime Medical Information for Man

3. When searching the OMIM database, only one search term is accepted at a time.
   a) True
   b) False

4. By searching the OMIM electronic database, you can obtain information regarding:
   a. the pathogenesis and mode of inheritance of a disorder
   b. the findings associated with a disorder
   c. accessing a lab that can help confirm the working diagnosis of a disorder
   d. (a) and (b)
   e. all of the above

5. At the recent endocrinology meeting you heard someone mention that mutations in the *PTEN* gene caused thyroid disease, along with breast and ovarian tumors in some families. Which of the following conditions is caused by PTEN mutations?
   a) Carney complex
   b) Congenital adrenal hyperplasia
   c) Cowden disease
   d) Marfan syndrome
   e) Multiple endocrine neoplasia

Answer Key: 1. a 2. a 3. b 4. e 5. c

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Adult Consequences of Pediatric Endocrine Disease, I: Congenital Adrenal Hyperplasia

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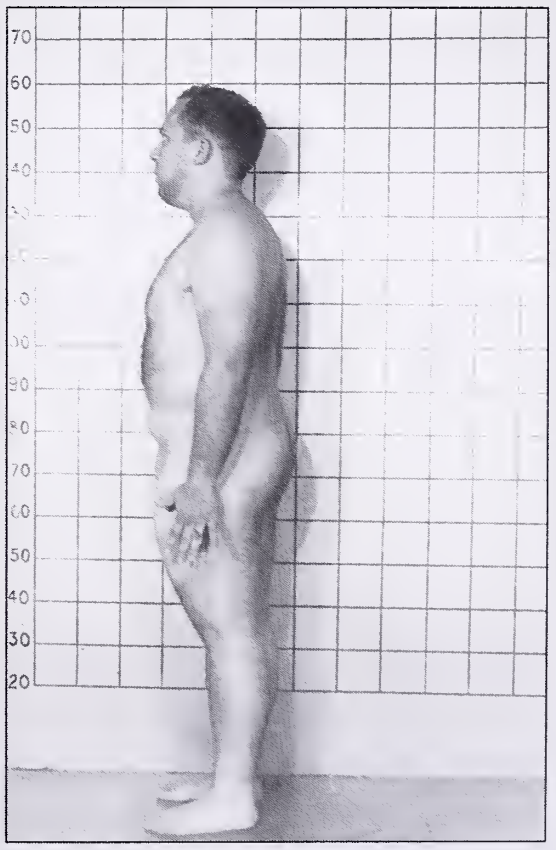
Before 1950, congenital adrenal hyperplasia (CAH) was characterized by marked virilization in females and sexual precocity in males. Salt-wasting with adrenal crisis was common. Wilkins et al (1950) and Barter et al (1951) independently reported that cortisone therapy placed the adrenals at rest and androgenic hormones fell to appropriate levels.[1,2] Salt-retaining corticosteroids usually controlled the salt-wasting.

The adult consequences of CAH in infants and children now can be evaluated. The purpose of this article is to relate what used to happen to CAH patients, what happens to infants who are treated with glucocorticoids, what happens to patients treated late in childhood, what difference early and adequate treatment may make when patients reach adulthood, and what possible alternative therapeutic approaches now can be considered and evaluated.

WHAT USED TO HAPPEN TO PATIENTS WITH CAH?

The salt-losers usually died. Consequently, it was the non-salt-losers who lived to adulthood. Exemplary of this is C.L., who as a newborn was thought to be a male with bilateral cryptorchidism and hypospadias. Following diagnosis of CAH at chronologic age (CA) of 6 years, height age (HA) of 9 3/12 years, and bone age (BA) of 12 years, an oophorectomy and hysterectomy were performed. In 1955, he appeared to be a very virile adult male (Figure 1), although his chromosomal karyotype was 46,XX. His genitalia was that of an adult male, although the testes were prostheses. C.L. married and had a heterosexual relationship compatible with his

Figure 1
C.L.: A 46,XX CAH Patient Raised as a Male



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In This Issue

This educational activity is supported by an unrestricted educational grant from Genentech, Inc.

phenotype. When last seen, he regarded himself as a male in every respect. This is an extreme example of what happened to CAH patients who were not treated until late.

A second example is Andrea (A.J.) at age 10 years (Figure 2, on the left), who subsequently was Andrew (Figure 2, on the right). CAH was diagnosed shortly after birth. Her poor rural parents were given cortisone to treat her, but they never returned to the doctor's office until she was referred at age 10. A.J.'s playmates questioned whether she was a male or a female. This exceedingly shy individual would talk with none of us except occasionally with Dr. John Money, the psychologist whose help was invaluable and historic. Dr. Money talked with her over a period of 6 months, and she was given the choice to decide whether she wished to remain a female or become a male. One day, A.J. wrote a note to each of her parents stating, "I gotta be a boy." And so he was. A phallic urethra was created and testicular prostheses were put in place. The last time he was seen, he was functioning as a male (Figure 3), although at 24 years of age he professed not to be sexually active.

These are the things that used to happen to patients with CAH. A tremendous amount has been learned from untreated patients such as these 2 and many others, particularly as they reached adulthood.

Figure 2
A.J.: A 10-Year-Old 46,XX CAH Patient Whose Sex of Rearing Was Changed at 10.5 Years

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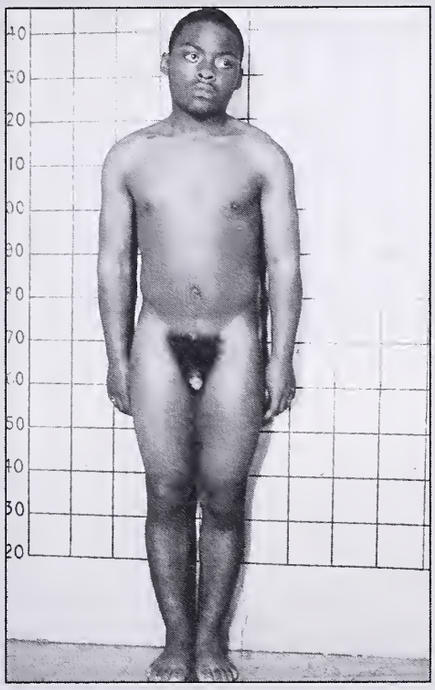
WHAT HAPPENS TO CAH PATIENTS WHO ARE TREATED WITH GLUCOCORTICOIDS WHEN INFANTS?

One of the first patients treated early was M.L., who was the firstborn child of tall parents. She had ambiguous genitalia and salt-wasting, and received cortisone in the first month of life starting in 1952. M.L. was appropriately treated—both surgically and medically. Surgically, the clitoris was removed and a vaginal orifice separate from the urethral orifice was created. The urinary 17-keto steroids were consistently in accord with adequate suppression. On physical examination there was nothing to suggest Cushing's syndrome, which could have stunted growth and resulted from overtreatment with cortisone. Her BA was consistent with her CA, but her HA throughout childhood was approximately 2 SD below the mean. She experienced no salt crises, indicating adequate

Figure 3
A.J. as 24-Year-Old Adult Male



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therapy with deoxycorticosterone acetate and salt. Regardless, she did not grow in accord with her genetic potential. As an adult, she is 160 cm tall, and is the smallest of her 3 unaffected female siblings, all of whom are very close to or above the midparental height (MPH) of 175 cm.

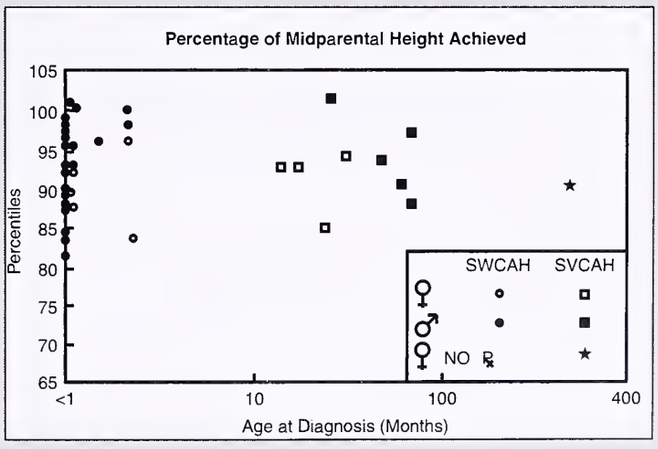
Thelarche occurred when M.L. was 13 years old. Significantly, menarche did not occur until 19.5 years. Her uterus was determined to be very small at age 19 years. Menses were not established with any regularity until she was 25 years of age. At age 35, M.L. married, but had been having unprotected intercourse for 10 years. She was not enthusiastic about assuming parental responsibilities, but did not avoid the possibility.

AUXOLOGIC CONSIDERATIONS OF THE CAH SYNDROME

The heights of CAH patients who are diagnosed early and treated in accord with what is believed to be "good treatment" are less than ideal or expected. Di-Martino-Nardi et al[3] summarized reports from 9 clinics regarding the ultimate height of patients with salt-wasting CAH (SWCAH) and simple virilizing CAH (SVCAH). Nearly all male and female patients who were studied ended up being shorter than expected. The percentages of MPHs achieved according to the age at diagnosis are plotted in Figure 4. Surprisingly, the age at diagnosis did not markedly affect the outcome, and there was little difference between patients with SWCAH and SVCAH. Conclusions reached by this group and others include the following: (1) The age at diagnosis did not correlate with ultimate height; (2) the quality of metabolic control did not seem to affect the ultimate height; and (3) SVCAH and SWCAH patients were equally below their target heights as adults and less than their first height prediction as a child. In another study, Mulaikal et al[4] reported that 40% (32 of 80 patients) were below the 5th percentile for height (Figure 5 page 36). Multiple authors have reported similar reductions in ultimate heights.[5-14]

The experience of some but not all reporting investigators[12,13] is that untreated SVCAH children are slow growing in the first year of life. The data of Clayton[8] demonstrate that the adolescent growth spurt is dwarfed. This has been confirmed in more recent studies. Decreased adult height has been correlated with increased body weight and body mass index (BMI) during childhood.[13,15-17] Clayton's data[8] indicate that both boys and girls with CAH are usually overweight for height.

Figure 4
Adult Heights of CAH Patients Diagnosed at Different Ages



SVCAH, simple virilizing CAH
SWCAH, salt-wasting CAH

Adapted with permission from DiMartino-Nardi, et al.[3]

Data regarding bone mineral density (BMD) are limited. Data from 2 reports concerning adults indicate no decrease in BMD among CAH patients who were receiving glucocorticoid therapy.[18,19] Guo et al[15] reported that BMD at various sites was not decreased although adult height was. In a third report,[19] BMD was decreased in adults on treatment (Figure 6 page 37). These authors evaluated 32 adult patients. BMD was evaluated in the left femoral neck and in the lumbar area with dual X-ray absorptiometry. BMD Z score was -0.52 (P=0.045) at L2-4

and -0.83 in the femoral neck ($P<0.001$). For both sites, there was significantly negative correlation between mean glucocorticoid doses and BMD (Figure 7 page 38). The comparable effects of various corticosteroids were reported. Hydrocortisone was preferable as therapy to prednisone, prednisolone, and dexamethasone.[20]

INTELLIGENCE AND BEHAVIOR IN CAH PATIENTS

The intelligence of CAH patients was initially reported in the 1960s to exceed genetic expectations. However, subsequent studies have found no increased intelligence. In 1991, Nass and Baker[21] reported that SWCAH patients have a lower IQ (107 vs 117) than SVCAH patients. They reported a greater incidence of learning disabilities among female patients than nonaffected females. A greater incidence of learning disabilities exists in normal male than in normal female children. It has been postulated that this is attributable to intrauterine exposure to androgens. The verbal performance IQ discrepancy (10.1) for 18 female patients was significantly greater than for 27 unaffected female sibs. A wider discrepancy exists in normal males than females. The data are compatible with intrauterine exposure to androgens by the CAH females.

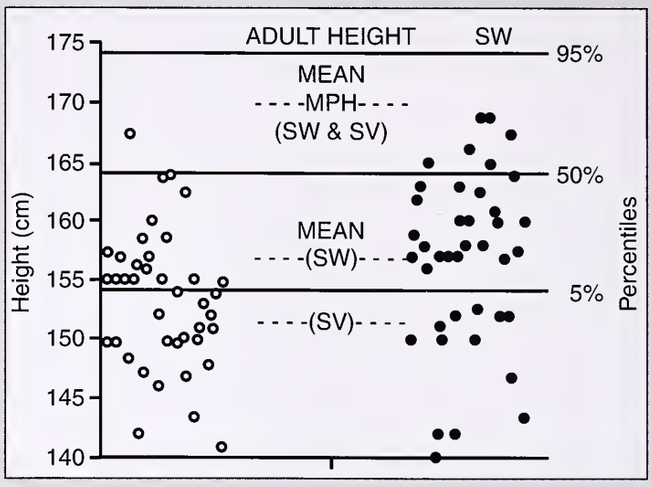
CAH males are more likely to show aggressive behavior than CAH females. In a well-controlled study with 3 different approaches, control males had higher aggression scores than control females, as predicted, but the difference was statistically significant only at adolescence and in adulthood. The scores of CAH females were more in accord with normal males than with normal female controls.

GENDER IDENTITY, GENDER ROLE, AND PSYCHOSEXUAL PREFERENCE

Gender identity, gender role, and psychosexual preference are not necessarily the same. Gender identity relates to whether one considers oneself a male or a female. Gender role relates to whether one acts as a male or a female regardless of what one's self-image is in respect to gender identification. An individual may have a gender identity of a female but play the role of a male in a modest sense, such as being a tomboy, or in a full sense, such as being masculine in characteristics and playing the male part in a lesbian relationship. A tomboy is defined as a girl who prefers to wear jeans to dresses, play football rather than jump rope, fish rather than play dolls, be dusty rather than clean, and climb trees rather than go shopping. Psychosexual orientation or preference is reflected by homosexuality, heterosexuality, or bisexuality.

To best study gender identity, gender role, and psychosexual orientation in CAH patients, it was necessary to study not only patients treated with glucocorticoids since infancy but also those who were not treated until much later. Exemplary were patients who were not treated until late childhood or adulthood, reported in 1968 by Ehrhardt, Evers, and Money.[22] These authors reported on the influence of androgens on various aspects of sexually dimorphic behavior in women with CAH who were treated late, ie, after 8 years of age. The purpose of their study was to see if exposure to androgens fetally and/or in childhood and/or later produces sexually dimorphic behavior. Twenty-three women met the sampling criteria. Their ages ranged from 8 to 47 years, with a mean of 26 years. A majority had lived for many years with the stigma of heavy virilization and some with uncorrected genital morphology. Most lacked female secondary sexual characteristics such as breast development. With initiation of therapy in this older group, breast development and menstrual periods began, usually within 3 to 6 months. There are, however, exceptions (see M.L. case). Their sex drive and sexual practices, gender identification, gender role, and psychosexual orientation were quite revealing. Ten of the 23 were married. Eight of these were heterosexual and 2 bisexual. Twelve (approximately 50%) had engaged in heterosexual activities exclusively, although 5 of these reportedly had homosexual fantasies. A surprising 11 had either homosexual fantasies, homosexual dreams, or both. Sex drive was high in 11 of 23. Orgasm had occurred in 4, even though the clitoris had been removed. The incidence of homosexual inclinations, the erotic response to visual material, and their personal freedom in sexual activity indicated behavior more often found in males than in females. The authors concluded that the androgens in utero must be responsible for the male-like activity since normal female fetuses who were exposed to placental transfer of synthetic progesterones, which were derivatives of

Figure 5
Heights of 80 CAH Females in Adulthood



MPH, midparental height
SV, simple virilizing
SW, salt-wasting

Reprinted with permission from Mulaikal, et al.[4]

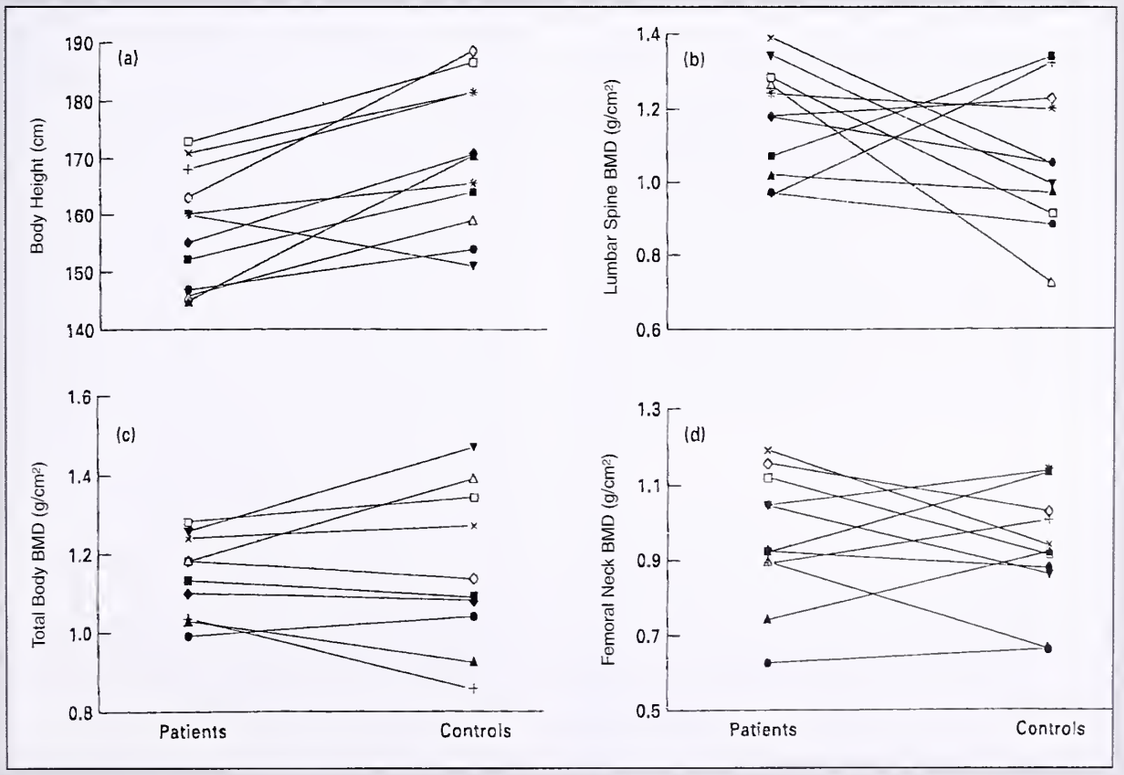
testosterone, had ambiguous genitalia and gender roles similar to the patients with CAH. This paper[22] was one of the first to suggest that male behavior traits were increased in female CAH patients. Many other publications up through 1997 have confirmed these findings, including an outstanding article by Zucker et al.[23]

In 1984, Money et al[24] wrote about adult heterosexual status in relation to fetal hormonal masculinization and demasculinization. This excellent study compared 30 46,XX CAH patients who were treated at CA >8 years and a control group of 27 consisting of 15 patients with androgen insensitivity and 12 46,XX females with the Rokitansky-Küster-Hauser syndrome, meaning congenital absence of the uterus.

In Table 1 (page 39), 37% of the individuals with CAH were rated as bisexual or homosexual in contrast to the 7% incidence in the controls. The 7 who were noncommittal are suspected of having a bisexual or homosexual orientation, as they would not commit themselves to a response. If these 7 are eliminated from the statistics and the data based on the 23 remaining patients with CAH who committed themselves in their responses, homoerotic arousal imagery by age 20 was present in 48%, in contrast to 7% of the controls and to 15% of the general female population sample from the Kinsey report. Twenty-two percent of the 23 had had a homoerotic partner contact by age 20 in contrast to 4% of the androgen insensitivity patients. Data in this report confirmed and extended earlier data reported by Ehrhardt and colleagues.[22,25,26] Dittmann et al[18,27-29] demonstrated that prenatally androgenized CAH patients, even when treated soon after birth, differed significantly from sisters of CAH patients and from controls. These CAH children, although identifying primarily as females in respect to their gender identity, were much more oriented towards activities that interest boys than girls. Comparisons were remarkable when these patients were compared with their normal sisters. Sixteen of 29 single items used for testing suggested significant differences between the 2 groups of girls. In all CAH patients, there was a stronger male orientation than in their unaffected sisters. The patients with SVCAH were less male oriented than the SWCAH patients, and similar although not as markedly feminine as their unaffected sisters. The salt-wasters were oriented markedly towards the male end of the scale. Since androgens are present in utero in both SWCAH and SVCAH patients, the difference between these 2 groups is not explained readily.

Dittmann et al[18] compared 34 adult CAH patients to 14 sister controls, focusing on the psychosexual development

Figure 6
Bone Mineral Density (BMD) of CAH Patients on Therapy Versus Controls. Various Symbols Reflect Paired Patients With Controlled Patients for Size, Age, Etc.



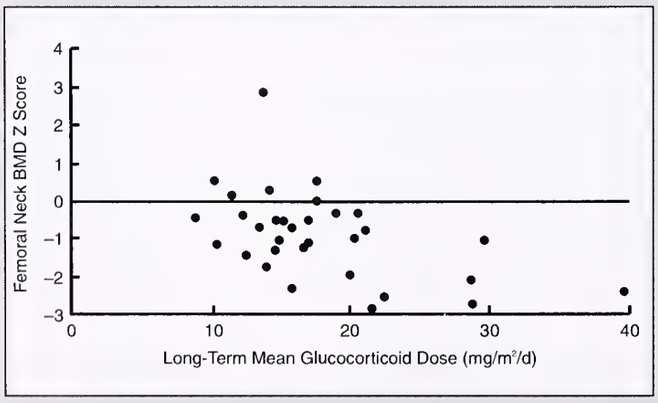
Reprinted with permission from Guo CB, et al.[15]

and sexual orientation of the 2 groups. Significantly fewer patients than sisters had ever experienced love relationships and/or sexual activities with male partners. Twenty percent of the patients and none of the sisters wished for and/or had homosexual relationships. In patients >21 years, 44% expressed this interest. Patients with SWCAH differed significantly more from their unaffected sisters than did the SVCAH females from their unaffected sisters. These results corroborate earlier reports on both delays in reaching psychosexual milestones and increased rates of bisexual/homosexual fantasies and experiences in CAH women.

A study contributing to the concept that 46,XX CAH patients raised as males are male oriented was published in 1976 by Money and Dalery.[30] In this study, the authors compared the gender identities, gender roles, and psychosexual orientation of 3 46,XX CAH patients who had complete differentiation of the external genitalia along male lines and who were raised as males with the same parameters of 4 similar patients who were assigned as females at 6 days, 19 days, 8 weeks, and 1 year of life. The 3 reared as males were last studied as adults. Those raised as females were last studied in late childhood.

Evaluation of the data (Table 2) reveals certain common patient characteristics in the 2 groups during infancy and childhood. The data concerning the 4 raised as females are in the right column and the data concerning the 3 raised as males are in the left column. All 7 played with dolls rarely. They preferred traditional boys' toys such as trucks, guns, and blocks. All 7 had a lack of interest in infant caretaking. All 7 exhibited high-energy expenditure and rough outdoor play. All 7 preferred boys over girls in peer contact, and they liked competition with boys. All were oriented toward clothes appropriate for tomboys. The 4 raised as girls, although tomboyish, did not have an overt desire to be boys. All 7 were able to mix with and be accepted without difficulty by their age-mates in all settings. Study of the 3 raised into adulthood as males revealed all functioned as males sexually. Two of the 3 were married and the third anticipated marrying. The wives of the 2 already married reported being satisfied with their partner's sexual function. None reported any erotic behavior or fantasies toward men. More recent studies[13,14,31,32] confirm that 46,XX CAH females have a greater than expected propensity to accept or request being raised as males, even some at adolescence or post adolescence.

Figure 7
Bone Mineral Density (BMD) Versus Long-Term Glucocorticoid Therapy



Reprinted with permission from Jääskeläinen and Voutilainen.[20]

If androgen exposure is interrupted at birth—as in the case of the 4 girls reported above who were assigned to the female sex, who were reared as girls, whose genitalia was surgically corrected to female, and who experienced a feminizing puberty—establishment of a female gender identity occurs. However, the gender role and psychosexual preference is often male oriented. Both the fetal hormonal milieu and the postnatal environment, including sex assignment, may play important roles in gender identity. Very rarely does a 46,XX CAH patient raised from early infancy as a male elect to have the sex of rearing changed to that of a female.

Gender identity, gender role, and psychosexual preference of 46,XY individuals with CAH are uniformly in accord with those of most 46,XY males, as might be expected from intrauterine exposure to excessive androgens.

PREGNANCY IN CAH FEMALES

The incidence and prevalence of pregnancy in SWCAH females is very low compared with that in SVCAH patients. Mulaikal et al[4] reported on 80 adult female CAH patients (40 with SWCAH and 40 with SVCAH). Twenty-five pregnancies were reported among 15 women with SVCAH, but only 1 pregnancy was recorded in 40 patients with SWCAH. In the Cardiff experience[5] of 16 patients (11 SWCAH, 5 SVCAH), a 40% ovulation rate, as measured by salivary progesterone, was found. Three of 5 patients with SWCAH and 2 of 3 patients with SVCAH who had both an adequate introitus and were sexually active produced 8 pregnancies. This study highlights the potential for improved fertility in compliant patients who are treated early, who have adequately reconstructed genitalia, and who are followed closely during pregnancy for progesterone, 17α-hydroxyprogesterone, and testosterone levels. A 1998 review by Garner,[16] entitled "CAH in Pregnancy," provides an overview of CAH in both mothers with and without CAH and in potential CAH fetuses in utero. More information on the frequency of pregnancy in SWCAH is very much needed, but the pregnancy rate certainly is low from all data presented to date.

What are the possible causes of the difference in pregnancy rates in SVCAH and SWCAH? The first possibility is that therapeutic noncompliance is greater among SWCAH patients. The second possibility is that there is

Table 1
Data Regarding 30 46,XX CAH Patients Diagnosed at >8 Years and a Control Group of 15 Androgen Insensitivity (AIS) Patients and 12 46,XX Females With Rokitansky-Küster-Hauser Syndrome (RS)

Comparison of Homoerotic Incidence in CAH, AIS/RS, and Kinsey's Sample at Age 20

	CAH N=30	CAH N=23*	AIS/RS N=27	Kinsey's Sample
Homoerotic arousal (imagery)	37%	48%	7%	15%
Homoerotic partner	17%	22%	4%	10%

*Omitting 7 noncommittal subjects.

Reprinted with permssion from Ehrhardt and Meyer-Bahlburg.[26]

a higher frequency of menstrual irregularity among SWCAH patients, reflecting less ovulation in this group. Third, there is a lower incidence of marriage in the SWCAH patients than in the SVCAH patients and, therefore, there is less opportunity for pregnancy. Fourth, the vaginal introitus is more frequently inadequate in the SWCAH group compared with the SVCAH group (53% vs 18%).[15] Another possibility is that SWCAH patients engage in heterosexual activity less frequently.

The necessity for cesarean section[15] in patients with SVCAH is very high. Of the 15 females with SVCAH experiencing 25 pregnancies, 13 carried to term. Nine of these 13 required cesarean sections because of pelvic disproportion. This is not surprising because of the constrictive anatomy that often is present postoperatively.

In respect to the necessity for a clitoris or phallus to be present to effect orgasm, it appears that the clitoris is not essential although probably desirable. Ehrhardt et al documented this in 1968,[22] and my observations with several adult female CAH patients who have had total clitoridectomy confirmed that orgasm does occur in some patients in the absence of the clitoris. Meyer-Bahlburg and colleagues[31] and others[33] have confirmed that the clitoris is desirable but not essential for orgasm. Vaginal sensitivity seems to be adequate for orgasm to occur in many.

THERAPEUTIC CONSIDERATIONS

Therapeutic approaches are designed to ameliorate the adult consequences of CAH. As in the past, most current therapy is directed toward salt loss in SWCAH and toward controlling the excessive production of adrenal androgens and correcting reduced cortisol production with glucocorticoids. The question whether continued glucocorticoid therapy is necessary in 46,XY males who reach adulthood is often raised. In some male patients, stopping therapy produces development of testicular tumors (adrenal rests). The tumors histologically appear as testicular tissue but do not have Reinke crystals. These crystals are found in testicular tissue and differentiate Leydig cells from adrenal cells. Orchiectomies have been performed unnecessarily by uninformed physicians. Adrenal rest tumors of the ovary also occur. Adequate glucocorticoid therapy prevents the development of adrenal rest tumors.

Gonadal failure and infertility have been documented in males when glucocorticoid therapy was stopped. Some untreated patients with resultant gonadal suppression by adrenal androgens take more than 2 years to develop spermatogenesis. Urban et al,[6] however, noted that 19 of 20 adult males, 7 untreated at the time, had normal sperm counts. Variation among patients probably occurs in relation to the extent of hyperandrogenicity.

Adrenal tumors,[17] some of which are malignant, have been reported. These result from hyperactivity in the nonsuppressed gland. In addition, hyperandrogenicity may produce overt aggression, hostility, violent temper explosions, and inability to handle the slightest frustration in males; one case in association with an adrenal rest tumor of the testes also has been reported.[17,34] All symptoms disappeared with adequate glucocorticoid treatment and reappeared when compliance waned.

There is ample evidence that for many reasons treatment should be continued in male and female CAH patients throughout adulthood.[35]

Table 2
Data Regarding 7 46,XX Females (3 Raised as Males and 4 as Females From Birth): Characteristics of the 2 Groups

Characteristic	Rearing 3 as ♂	Rearing 4 as ♀
Rarely played with dolls	3	4
Played with guns, trucks	3	4
Interest in infant and child care	0	0
High energy at play	3	4
Preferred male peers	3	4
Preferred male clothing	3	4
Wished to be opposite sex	0	0
Accepted by playmates	3	4

Reprinted with permission from Money and Dalery.[30]

Innovative approaches recently have been considered, including total adrenalectomy. Van Wyk et al[36] suggest this approach in at least some female patients for the following reasons:

- Many CAH patients have adrenals that are deficient in producing hydrocortisone and aldosterone.
- Infertility and hirsutism may be related to increased adrenal production of progesterone and/or androgen even when endogenous or exogenous hydrocortisone levels and urinary ketosteroids are normal.
- Medical treatment that is successful requires physiologic doses of hydrocortisone and not the pharmacologic doses now usually used in attempting to control androgen production. Decreased hydrocortisone treatment as a result of adrenalectomy could produce greater height.
- In the opinion of some authorities, the mortality risk for CAH patients could be less than with medical treatment.

At least 20 of 158 female patients receiving medical treatment at The Johns Hopkins Hospital died of their disease, which is an impressive number. Recent personal communication with Van Wyk indicates that several respected pediatric endocrinologists have successfully utilized adrenalectomy in selected patients as a form of therapy. Personally, I believe this therapy has a role in selected cases and potentially in many more than currently are being treated in this manner.

In respect to alternative medical therapy, Laue et al[37] at the National Institutes of Health (NIH) have proposed the combined use of flutamide (an androgen receptor blocker), testolactone (an aromatase inhibitor), and decreased doses of hydrocortisone. While theoretically logical, I agree with Dr. C.J. Migeon of Johns Hopkins that we need less therapy because we need more compliance. More medications will usually lead to less compliance. Therefore, I am not optimistic about the NIH proposal, although further studies currently being carried out need to be completed for appropriate interpretation.

Arguments that are presented against performing adrenalectomy include: (1) Medical treatment is less invasive; (2) medical treatment very possibly is less threatening to life than adrenalectomy; (3) preserving the adrenals provides potential for other types of treatment in the future; and (4) medical therapy as proposed by Laue et al[37] may provide a better approach to therapy than those we now have.

Dexamethasone treatment of the female CAH fetus in utero, via the pregnant mother, is still debated after 18 years of use. A recent debate[38] by several prominent pediatric endocrinologists offers an excellent summation of current thinking. The contributors were Dr. M. Forest, who is a promoter of this form of therapy; Dr. W. Miller, who is conservative in considering this therapy; and Dr. M. Ritzen, who gave a favorable commentary on its use.

The results of treatment as reported by Forest are as follows: (1) Treatment is effective and has been used in more than 110 mothers; (2) maternal side effects are bothersome in approximately 9% to 30% of mothers receiving dexamethasone for this purpose, but the etiology of many of these side effects may be the pregnancy itself; (3) no teratogenic effects have been noted; (4) no inhibition of growth in utero, in childhood, or adolescence has been reported to date; and (5) regarding the effects of dexamethasone on the brain and its development, the only possible effect that has been reported is mild temperament alterations in a few patients.

The stated arguments[38] against the use of dexamethasone treatment were fourfold:

(1) Only 1 of 8 fetuses treated initially in utero are treated long term but all 8 are exposed to dexamethasone at a critical time in utero. These statistics exist because 4 of 8 fetuses treated will be males; the other 4 will be females but only 1 of these will have CAH and require continuing treatment. Unfortunately, treatment has to be given before the sex of the fetus is known, and, therefore, all fetuses must be treated starting at a very early age before differentiation of the external genitalia occurs.
(2) The dexamethasone dose is pharmacologic, not physiologic.
(3) The effect of dexamethasone on the fetal brain may be unknown.
(4) The safety of acute withdrawal of dexamethasone in 7 of the 8 fetuses after 4 to 5 weeks of treatment is of concern.

Ritzen[38] countered in his commentary, noting that the risk for increased abortion is not significant; intrauterine and postnatal growth are normal; the effects on the fetal brain are not significant, as reported to date; and, while there are some mild maternal side effects during pregnancy, no significant long-term effect has been reported. He agrees with Miller that well-controlled, prospective, multicenter studies are needed and that patients should be treated only under a well-designed protocol.

CONCLUSION

Forty-eight years of study of CAH patients have passed since CAH was first effectively treated. Many challenging questions have been raised, and many have been answered. These cover the transition of patients with CAH from early fetal development to infancy, to adolescence, and then to adulthood. This review is presented to historically record the effect of CAH and its treatment on the mature individual with CAH. A second goal is to emphasize that challenges still exist for clinical investigators.

This manuscript is dedicated to Lawson Wilkins, whose intellectual curiosity stimulated so many of his colleagues and students to continue to ask questions and find the answers to the pathophysiology and treatment of congenital adrenal hyperplasia.

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An extended list of references will be supplied upon request. Address to: *GGH*, Dr. R. Blizzard, 1224 West Main Street, Suite 701, Charlottesville, VA 22901. Telephone: 804-977-8192. Fax: 804-977-9450. E-mail: rblizzard@compuserve.com.

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Abstracts From the Literature

Reconstructing a Human Limb

The vertebrate limb is a very complicated structure whose development is extremely complex. Much has been learned in recent years; however, most articles, even review articles, are not written for clinicians. Bamshad and colleagues at the University of Utah have now assembled a clinician-oriented review that provides many important insights into how human limbs develop and how disturbances that lead to limb defects may arise.

The review covers many areas. It describes how the limb originates in the early embryo and how it grows to its final form. It presents the major actors in the process, many of which have been recently identified because mutations have been detected in patients with limb defects. A few examples include Greig's cephalopolysyndactyly and Pallister-Hall syndromes, which are due to mutations of *GLI3;* ulnar-mammary and Holt-Oram syndromes, which result from *TBX3* and *TBX5* mutations, respectively; Hunter-Thompson and Grebe syndromes, which are caused by *CDMP1* mutations; and Aarskog syndrome due to *FGD1* mutations.

Particular attention is given to 3 groups of genes. *HOX* genes encode transcription factors that contain a 60 amino acid DNA-binding domain called a homeodomain. There are 39 *HOX* genes in humans; these are organized into 4 clusters. *HOX* gene products partly control patterning of many different embryonic structures, including the limbs, where they may subdivide the limb into specific domains and activate downstream genes contingent upon the position of the domain along different axes.

TBX genes also encode transcription factors that share a DNA-binding domain called a T-box. At least 5 *TBX* genes are differentially expressed in the developing limb. In the chick and mouse, *Tbx5* and *Tbx4* are exclusively expressed in the forelimb and hindlimb, respectively, suggesting that they specify or at least influence limb identity. *GLI3* encodes a zinc-finger transcription factor. It seems to have both transcriptional activator and repressor activities. The clinical phenotypes that result from *GLI3* mutations are thought to reflect the combination of these activities that are disturbed. Finally, the authors address the evolutionary aspects of limb development.

Bamshad M, et al. *Pediatr Res* 1999;45:291-299.

Editor's comment: *This is a very complete review of the last decade of progress in vertebrate limb development. This review is for the clinician and nonclinician alike and provides considerable insight into the physiology and pathophysiology of limb embryogenesis. The latter is key to understanding physical developmental defects.*

One can divide limb development into 2 phases: an early phase during which the essential elements of the limb are formed and a later phase during which the limb grows to reach its final form. This review focuses on the former. Hence, the genes that influence patterning produce the syndromes that reflect defective patterning when mutations occur. In contrast, genes involved in the growth phase are those mutated in osteochondrodysplasias (growth phase defects).

William A. Horton, MD

Growth of Long-Term Survivors of Liver Transplantation

Viner et al performed a retrospective analysis of growth of 105 children who were long-term survivors of liver transplantation. During the 10-year period of the study, triple immunosuppression therapy using cyclosporine, azathioprine, and prednisolone was used. Height was recorded at all clinic visits using a Harpenden stadiometer. Following transplantation, height was recorded every 3 months for the first 18 months, twice a year for the next 3 years, and then yearly thereafter. Height is expressed as height Z scores (height SD scores) standardized against 1990 British growth references. Severe growth retardation was defined as a height below the 0.4 percentile. Continuous variables were analyzed by paired-tests and multiple regression analysis.

The height of patients at transplantation was significantly below that of the general population ($P<0.0001$), with the height Z score at -1.22. Following liver transplantation, height Z scores fell significantly in the first 6 months ($P<0.006$) but catch-up growth then occurred and was maximal from 6 months to 2 years. Height Z score at transplantation predicted 64% of the variance in height SDS at 2 years and 53% of the variance in height SDS at 5 years. Of 19 patients who were severely growth retarded, half remained so 4 years posttransplantation. Final height was recorded for only 14 patients, but their mean height SDS was -0.55. Diagnosis was not significantly associated with height Z scores at the time of liver transplantation (6.1 ± 4.4 years). Subjects undergoing transplantation who were less than 2 years old had significantly greater growth retardation at 6 months following transplantation ($P< 0.05$) and a trend towards greater catch-up growth from 6 months to 2 years. Multiple regression analysis demonstrated that predictors for height Z scores at 6 months were initial Z scores and bilirubin at transplantation and prednisolone dose at 6 months. At 4 years, height Z scores were predicted by height Z scores at transplantation and the cumulative dose of prednisolone at transplantation. Age, sex, diagnosis, liver function at transplantation, cyclosporine dose, and the need for retransplantation were not predictive.

The authors state that this was the first report of long-term growth and final height after liver transplantation in children. They note that their patients were a heterogeneous group and that transplantation in infancy was not associated with poor height outcome. The average final height after liver transplantation was on the 27th percentile. They suggest that further investigation of the use of corticosteroids prior to transplantation is needed, and that an attempt should be made to transplant children at earlier ages.

Viner RM, et al. *Arch Dis Child* 1999;80:235-240.

Editor's comment: *This is an interesting and fairly complete retrospective analysis. A summation is in the box that follows. The authors point out 2 very important questions for further study. First, how can corticosteroid doses be minimized prior to the time of transplantation such that the cumulative dose would be less at that time? Second, what is the role of hepatic-derived growth factors in the findings? Whether exogenous growth hormone might have a role in preventing growth retardation prior to transplantation is an additional area for further study and speculation.*

William L. Clarke, MD

Key Findings of the Retrospective Analysis of 105 Long-Term Survivors of Pediatric Liver Transplants

- Average final height after liver transplantation was on the 27th percentile, although those undergoing transplantation as infants can achieve better final heights.
- Height at transplantation is the most important predictor of later height outcome, emphasizing the need for optimal transplant timing and preoperative nutritional management.
- High corticosteroid dose, poor liver function, and the need for a second transplant were associated with poor height outcome.
- Transplantation in infancy was not associated with poorer height outcomes.
- Normal pubertal progress was resumed 3 to 5 years after transplantation.

Prolongation of Ovarian Lifespan Into Advanced Chronological Age By Bax-Deficiency

In both humans and mice, there is a marked excess of primordial ovarian follicles that degenerate early in life. The remaining oocytes appear to go through apoptosis over the lifetime of the individual female, leading usually during the fifth decade of life to menopause in women and to infertility 3 to 6 months before death in female mice. Bax-deficient female mice (ie, deficient in the normal Bax protein) have been found to have an increased number of primordial follicles in their ovaries compared with wild-type littermates. This excess of follicles is maintained into advanced age. In addition, the Bax-deficient mice possess hundreds of ovarian follicles that are in different stages of development. The aged Bax-deficient females fail to become pregnant. However, it appears that this is due to failure of the pituitary axis rather than nonfunctional oocytes because these mice can be superovulated and oocytes remain that are competent for in vitro fertilization. This suggests that the increased number of oocytes are competent for producing embryos even though assisted reproductive technology may be needed in old age. Careful morphometric analysis shortly after puberty of the numbers and structure of nonatretic follicles in wild-type and in Bax-deficient mice revealed approximately 3 times the number of nonatretic primordial follicles in the latter, suggesting that Bax-deficient mice do not go through the normal apoptotic process seen in normal mice and normal human females.

Perez GI, et al. *Nature Genet* 1999;21:200-203.

Editor's comment: *This observation in Bax-deficient mice has enormous ramifications for infertile women and suggests that there may be a mechanism to maintain oocytes in Turner syndrome and some familial types of ovarian degeneration. Perhaps developing a block to the normal Bax protein could maintain normal viable oocytes. Fortunately, this manipulation should be possible in mice and yet have great application in humans.*

Judith G. Hall, MD

Association Between Type I Diabetes and Haemophilus Influenzae Type B Vaccination: Birth Cohort Study

The temporal association between *Haemophilus influenzae* type b (Hib) vaccination and the development of type I diabetes in Finland was studied. The risk of type I diabetes was compared among 3 Finnish birth cohorts: those born within 24 months before the Hib vaccination trial (ie, historical controls); those vaccinated at 3 months of age and with a booster at 14 to 18 months of age; and those vaccinated only at 24 months of age. The unvaccinated cohort included 128,936 children; the 2 vaccine-eligible cohorts totaled 116,352 children. No significant differences were found at any time during the 10-year follow-up in risk of type I diabetes between the children born before the vaccination period and those vaccinated at the age of 24 months only (risk ratio 1.01; *P* 0.228). The difference in the risk between children vaccinated first at the age of 3 months and those vaccinated only at the age of 24 months also was not statistically significant (risk ratio 1.06; *P* 0.545). The authors conclude that "based both on randomized design and on the use of historical controls," it is unlikely that Hib vaccination or its timing is related to type I diabetes in Finnish children.

Karvonen M, et al. *Br Med J* 1999;318:1169-1172.

Editor's comment: *Insulin-dependent diabetes mellitus (IDDM) has been increasing in Finland over the last 3 decades. In children under 14 years of age, there has been a 2% to 5% per year increase, with a prevalence of 45/100,000 reached in 1996. This incidence is perhaps one of the highest in the world. During this period, children also were given an increased number of vaccines, including Hib immunizations. However, this study provides ample evidence that the concomitant expansion of Finland's childhood immunization program, at least in regard to Hib, is not responsible for the increased incidence of IDDM. The temporal association between the 2 variables does not seem to indicate that there is a cause-and-effect relationship. Unfortunately, the media, including a major segment on "ABC World News" on September 25, 1998, have reported on the alleged association between Hib vaccine and the development of this disease. I wish that the report by Dr. Karvonen and colleagues would receive equal time so that the public would not be needlessly concerned. The beneficial effects of Hib vaccination are well proven, and it would be unjustified to restrict vaccination because of potential adverse consequences that have not been proven to exist.*

In addition, other studies have found no increase of type I diabetes in association with various vaccines used in childhood, including measles, BCG, and pertussis vaccines.

Fima Lifshitz, MD

Blom L, Dahlquist G. *Diabetologia* 1991;34:176-181.
Dahlquist G, Gothefors L. *Diabetologia* 1995;38:873-874.
Heijbel H, et al. *Diabetes Care* 1997;20:173-175.
Parent M-E, et al. *Diabetes Care* 1997;20:767-772.

Cow's Milk Formula Feeding Induces Primary Immunization to Insulin in Infants at Genetic Risk for Type I Diabetes

Insulin autoantibodies (IAAs) often appear as the first sign of islet cell autoimmunity in prediabetic children. Because cow's milk contains bovine insulin, the authors followed the development of insulin-binding antibodies in children fed with cow's milk formula. Bovine insulin- and human insulin-binding antibodies were analyzed by enzyme immunoassay (EIA) and IAAs were analyzed by radioimmunoassay (RIA) in 200 infants carrying *HLA-DQB1*0302* but no protective alleles. These children participated in a Finnish population-based birth cohort study. Based on the prospectively registered information, the first 100 infants (group 1) enrolled in the study who were exposed to cow's milk formula before age 12 weeks and the first 100 infants (group 2) enrolled in the study who were exclusively breast-fed for longer than the first 12 weeks of life were selected for the present study. Also studied were 11 children from the 200 infants who had developed at least two diabetes-associated autoantibodies, 98 children with newly diagnosed type I diabetes, and 92 healthy children. The authors reported that the amount of IgG antibodies binding to bovine insulin was higher at age 3 months in infants who were exposed to cow's milk formula than in infants who were exclusively breast-fed before and at 3 months of age (median, 0.521 vs 0.190; $P<0.0001$). The antibodies binding to bovine insulin cross-reacted with human insulin. None of these infants tested positive for IAAs. The levels of bovine insulin-binding antibodies declined in both groups at age 12 and 18 months; in the 11 children with at least two diabetes-associated autoantibodies, the levels increased during the follow-up period ($P<0.0001$). IgG antibodies correlated with IgG2 antibodies binding to bovine insulin ($r=0.43$, $P=0.004$) and IAAs ($r=0.27$, $P=0.02$) in diabetic children, but not in healthy children.

The authors concluded that cow's milk feeding is an environmental trigger of immunity to insulin in infancy that may explain the epidemiologic link between the risk of type I diabetes and early exposure to cow's milk formulas. This immune response to insulin may later be diverted into autoaggressive immunity against beta cells in some individuals, as indicated by these findings in children with diabetes-associated autoantibodies.

Vaarala O, et al. *Diabetes* 1999;48:1389-1394.

Editor's comment: *Many studies have linked cow's milk consumed by infants to subsequent diabetes. The association is*

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based on animal experiments or indirect evidence derived from studies in which parents of diabetic children tried to recollect when their babies first started drinking milk-based formula.

The Finnish researchers who conducted this study avoided the vagaries of poor recall by studying children from birth. In so doing, they have added to the case against cow's milk. By monitoring infants in diabetes-prone families, namely, those with HLA-DQB1*0302*, the scientists found that infants getting cow's milk formula were more likely to develop the immune reactions associated with insulin-dependent diabetes mellitus (IDDM) than infants fed exclusively human milk.*

It is known that having one type of autoantibody to insulin indicates that a child has roughly a 40% chance of developing type I diabetes within the next decade. Additionally, having more types of these autoantibodies may be a sign of greater risk; having 3 types of autoantibodies imparts an 80% to 90% likelihood of developing type I diabetes. However, the precise cause of IDDM remains unclear. The children in the study were genetically predisposed to IDDM, but most will never get the disease. Something in the environment or diet, such as consuming cow's milk during infancy, may be a triggering factor.

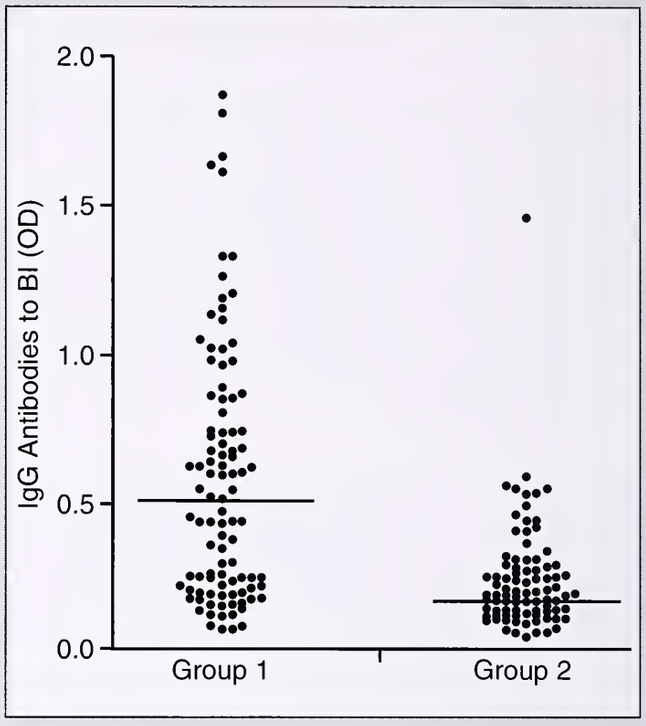
This study presents further evidence implicating cow's milk. In Puerto Rico, fewer than 5% of mothers breast-feed their children. Instead, nearly all use formula made from cow's milk. Meanwhile, the IDDM incidence in Puerto Rico is roughly 10 times the rate seen in Cuba, where breast-feeding is nearly universal. Such findings represent circumstantial evidence suggesting that ingestion of cow's milk in the first few months of life plays a very important role in the etiopathogenesis of this disease.

To date, none of the data on cow's milk and IDDM preclude feeding cow's milk formula to infants who do not have the good fortune of being fed human milk.

Fima Lifshitz, MD

Figure

The Levels of IgG Antibodies to Bovine Insulin (BI) at Age 3 Months in Infants Who Received Cow's Milk Formula Before Age 12 Weeks (Group 1) and in Infants Who Were Exclusively Breast-Fed Until Age 12 Weeks (Group 2)



The median is marked with a line. $P < 0.0001$, group 1 versus group 2 (Mann-Whitney *U* test).

Reprinted with permission from Vaarala O, et al. *Diabetes* 1999;48:1389-1394.

A Molecular Pathway Revealing a Genetic Basis for Human Cardiac and Craniofacial Defects

The investigators have identified a gene that is deleted or mutated in patients with the DiGeorge association (DGA) of craniofacial and cardiovascular malformations. Specific defects include interruption of the aortic arch, truncus arteriosus, tetralogy of Fallot, defective immunocompetence, and hypoparathyroidism. These widespread anomalies have been attributed to a defect in the function of neural crest cells important for normal structural development. The vast majority of patients with DGA have a monoallelic microdeletion of chromosome 22q11.2. Noting that mice lacking the transcription factor *dHAND,* a factor necessary for survival of neural crest cells in the branchial arches, aortic arch, and right ventricle, have many of the anomalies present in DGA, these workers examined the genes that this protein regulates. They found it to regulate the human homologue of *Ufd1,* a gene that encodes a protease that degrades proteins linked with ubiquitin that is localized to the critical region of 22q11 associated with DGA. The investigators demonstrated that in mice, *Ufd1* was expressed in those tissues that are adversely affected in patients with DGA. In all 182 patients with DGA and deletion of 22q11, *UFD1L* was absent. In 1 patient with DGA but no apparent chromosomal anomaly, the investigators demonstrated monoallelic deletion of exons 1 through 3 of *UFD1L* with retention of exons 4 through 12 of this gene. In the same patient, there was partial deletion of an adjoining gene, *CDC45*, a cell cycle protein. However, this gene is widely expressed. Therefore, the authors suggest that monoallelic inactivation of *UFD1L*, either by gross deletion or more subtle mutation, may be responsible for DGA. They hypothesize that the failure to degrade an as yet unidentified, ubiquitinated protein adversely affects the development of those neural crest cells necessary for normal formation of craniofacial bones, heart, thymus, and parathyroid glands.

Yamagishi H, et al. *Science* 1999;283:1158-1161.

Editor's comment: *Although it remains possible and perhaps even probable that DGA and associated disorders found in*

patients with deletion of chromosome 22q11 are the result of loss of contiguous genes, the current report strongly implicates UFD1L *as a key gene in DGA. Examination of this gene in additional patients with DGA without visible microdeletions of 22q11 will be important. Ubiquitin is a 76 amino acid peptide that links to and apparently "tags" proteins before they are degraded by proteases associated with the nonlysosomal 20S proteosome.*

Recently, the gene that is mutated in Angelman syndrome (UBE3A) *has been found to encode a protein (E6-AP) that is a ubiquitin-protein ligase. (Interestingly, E6-AP also is a coactivator for the transcriptional activity of the human progesterone receptor, but this metabolic function of E6-AP is intact in patients with Angelman syndrome.) Thus, Angelman syndrome is likely to be another example of a disease resulting from accumulation of a toxic protein that escapes degradation by the ubiquitin-proteosome pathway of protein degradation. Thus is identified another class of disorders, the "ubiquitinopathies," a name suggested by Dr. A. diGeorge.*

Allen W. Root, MD

Fang P, et al. *Hum Molec Genet* 1999;8:129-135.
Nawaz Z, et al. *Molec Cell Biol* 1999;19:1182-1189.

The Molecular Genetics of Growth Hormone Deficiency

Proctor et al have written an excellent review of growth hormone deficiency (GHD) from a molecular genetic perspective. It is both comprehensive and extremely useful. The GH synthetic pathway is relatively well worked out, as is its relationship to pituitary releasing factors and insulin-like growth factor 1 (IGF-1). Between 5% and 30% of "idiopathic" GHD individuals have a first-degree relative who also is affected, suggesting that there is a genetic etiology for many cases of GHD. The known mutations and genetic forms of GHD are reviewed, including the pituitary-expressed genes that have an effect on GH synthesis and release. In addition, of course, there are primary GH mutations.

The molecular basis of GHD is now being defined in multiple families. More than 30 specific deletions are known. Deletions seem to be particularly predisposed to anti-GH antibody production. At least 10 specific mutations have been described in different parts of the *GH1* gene. Until now, no correlations between mutant genotype and clinical phenotype have been reported.

The GH gene lies in a family of GH-type genes. Their closeness provides potential mechanisms for mutagenesis through slippage. There are a series of *GH1* gene mutations, including deletions, autosomal recessive mutations, and autosomal dominant splice site and intronic mutations. The human GH *(hGH)* gene cluster includes 2 chorionic somatotropin hormone genes, a chorionic somatotropin pseudogene, and 2 GH genes; *GH1* is the important functional gene. Evolutionarily in nonprimate mammals, GH is encoded by a single gene.

There are several familial forms of combined pituitary hormone deficiency (CPHD). The *PIT1* gene (*POU1F1*) is associated with autosomal recessive and autosomal dominant inheritance. In addition, *PROP1* gene mutations lead to autosomal recessive CPHD. GH-releasing hormone receptor mutations also have been identified.

Proctor AM, et al. *Hum Genet* 1998;103:255-272.

Editor's comment: *This is an excellent review. There are 5 pages of references for those individuals trying to research the problem. The delineation of the mutations is complete. As the authors point out, the development of specific mouse models should lead to a better understanding of genotype-phenotype correlation, as well as mechanisms to avoid anti-GH antibody production.*

Judith G. Hall, MD

2nd Editor's comment: *This article is an absolute must to read and digest for both clinicians and researchers involved in the origin of GHD and/or GHD-like syndromes. Drs. Proctor and Cooper of the University of Wales and Dr. Phillips of Vanderbilt University are eminently qualified as world experts on this topic.*

Robert M. Blizzard, MD

Metabolic Effects of Discontinuing Growth Hormone Treatment

The authors serially determined the resting metabolic rate (RMR), fat mass, percent body fat, and total body bone mineral content (BMC) by skinfold measurements and/or dual X-ray absorptiometry after discontinuing the administration of human growth hormone (hGH). The treatment periods ranged from 1.7 to 11.8 years in 11 (4 female) adolescent patients (aged 14.5 to 18.5 years) with isolated GH deficiency (GHD) or multiple anterior pituitary hormone deficiencies (N=8). They found that these measurements were stable during the last year of hGH therapy but that RMR declined within 2 weeks after stopping hGH and remained low through the next year. In GHD patients, fat mass increased within 6 months after cessation of hGH therapy. (In 15 non-GHD control subjects, 5 of whom had been treated with hGH, these measurements did not change appreciably over 1 year.) Six months after hGH administration was halted, there was an inverse relationship between the changes in RMR and fat mass. BMC was normal in the GHD subjects upon completion of hGH treatment and did not change in the ensuing year. The investigators suggest that the short-term decline in RMR after discontinuation of hGH in subjects with childhood-onset GHD may identify those patients with persistent adult GHD who would benefit by reinitiation of hGH therapy.

Cowan FJ, et al. *Arch Dis Child* 1999;80:517-523.

Editor's comment: *These data demonstrate that discontinuing the administration of hGH in childhood-onset subjects with GHD leads to rapid decrease in RMR. This was predictive of a later increase in body fat content. The data suggest that measurement of RMR shortly after discontinuing hGH administration (Figure) may identify those patients who will benefit by restarting therapy for adult GHD. This hypothesis merits further testing.*

Of interest would have been presentation of data on insulin-like growth factor 1, insulin-like growth factor binding protein 3, and acid labile subunit values after discontinuing hGH, and analysis of the relationships of these measurements to change in RMR and body fat composition. The current data also demonstrate that prolonged treatment of GHD children and adolescents with hGH can prevent the osteopenia often associated with hypopituitarism.

Allen W. Root, MD

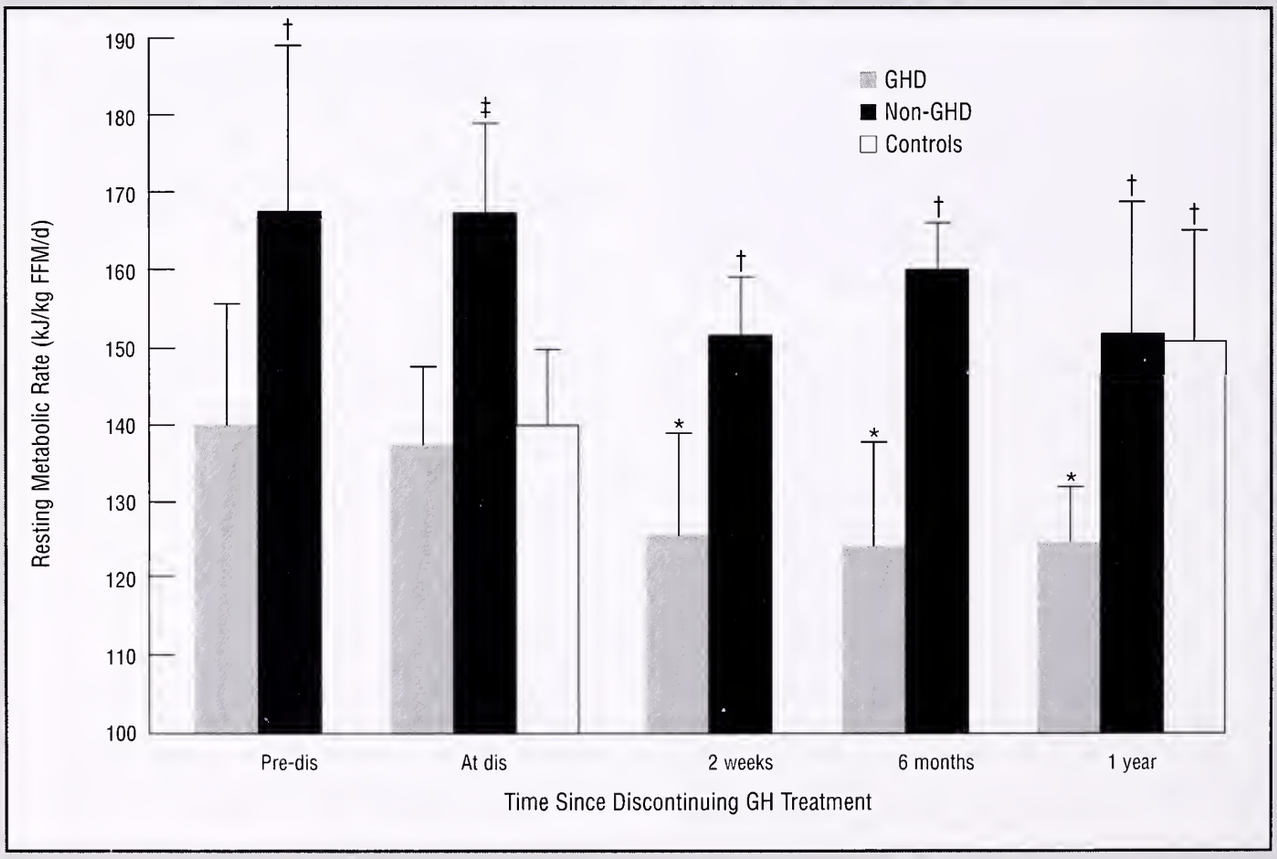
2nd Editor's comment: *This is an interesting and well-conducted study. The authors have pointed out that the serum GH criteria for replacing GH in adults is different from that in children, and that many treated children have relatively normal GH secretory responses to pharmacologic stimuli as adults. Thus, it is unclear which individuals should be considered for continuation of therapy.*

RMR measurements are not easy to perform, and their determination is not readily available in most clinics. Thus, even though these authors demonstrated some potentially important and very sensitive measurements that might help the physician decide which patient should continue GH therapy, it may not be possible for these data to be collected in many settings. It would be useful for all pediatric endocrinologists to know what happens to children who meet these criteria, and those who do not, who are subsequently treated with GH as adults. Until such data are available, physicians will most likely continue to rely on a myriad of subjective information to determine which individuals to retest and continue on therapy into their adult years.

William L. Clarke, MD

Figure

Mean (SD) Resting Metabolic Rate Before Discontinuing (Pre-dis) GH Treatment, at Discontinuation (At dis) of Treatment, and 2 Weeks, 6 Months, and 1 Year After Stopping Treatment



*$P < 0.01$ compared with values at discontinuation of GH treatment
†$P < 0.005$ compared with GHD group
‡$P < 0.05$ compared with GHD group and controls

Reprinted with permission from Cowan FJ, et al. *Arch Dis Child* 1999;80:517-523.

Female Development in Mammals by *Wnt-4* Signalling

Although differentiation of the testes and of male internal and external genitalia have long been known to be actively guided processes, it has been assumed that differentiation of the ovary and of female internal genitalia are "innate" processes that occur by default. Vainio et al demonstrated that in the mouse, ovarian and Müllerian duct differentiation are active processes influenced by the product of *Wnt-4,* a member of a family of extracellular, cysteine-rich glycoprotein signaling molecules (OMIM 603490). The latter influence a number of developmental processes, including normal renal development in the mouse.

Wnt-4 also is expressed in the embryonic gonadal ridge, the undifferentiated fetal gonad, the fetal ovary (although downregulated in the fetal testis), and in mesenchyme of the Müllerian but not the Wolffian ducts. By crossbreeding animals heterozygous for inactivation of *Wnt-4*, these investigators developed fetuses and newborns that were homozygous for this defect (*Wnt-4*$^{-/-}$).

The male offspring were phenotypically normal, but the female offspring were virilized. The ovary was deformed and the Müllerian ducts were absent. The single gonadal duct resembled an epididymis. The external genitalia of the female offspring were normal. The *Wnt-4*$^{-/-}$ female gonad appeared to synthesize and secrete androgens as it expressed both *HSD3B* and *CYP17*. The homozygous fetal ovary had far fewer oocytes than the normal ovary, suggesting that *Wnt-4* is necessary for oocyte maintenance. The investigators conclude that *Wnt-4* is important for normal fetal female sexual differentiation in the mouse and, by inference, in other mammals, possibly including humans.

Vainio S, et al. *Nature* 1999;397:405-409.

Editor's comment: *This study demonstrates the essential role that* Wnt-4 *plays in Müllerian duct differentiation and ovarian function. It is of interest that in the* Wnt-4$^{-/-}$ *females, Müllerian duct inhibitor factor from the Sertoli cells was not necessary for regression of the Müllerian ducts!*

It has been suggested that DAX1 *(dosage sensitive sex reversal on the X chromosome—Xp21) may be important for ovarian differentiation. The role of* DAX1 *in sexual differentiation has been demonstrated by the sex reversal of 46,XY males in patients with duplication of this gene, thus suggesting that this transcription factor is involved in ovarian determination and repression of testicular function. Yu et al (Role of Ahch in Gonadal Development and Gametogenesis.* Nature Genet *1998;20:353-357) generated a mouse model in which* Dax1 *has been inactivated. In these animals, ovarian differentiation and fertility are normal, but spermatogenesis and testosterone secretion in the male are disrupted. Thus,* Dax1 *affects testicular function in a dose-dependent manner; normally, it supports spermatogenesis and Leydig cell function, but when duplicated leads to inhibition of the testis-determining effects of* SRY *and* SOX9. *Embryologic sex differentiation becomes more complex as we learn more and more about gene control. We used to be able to explain sexual differentiation on a hormonal basis, but we cannot do this in 1999.*

Allen W. Root, MD

COL9A3: A Third Locus for Multiple Epiphyseal Dysplasia

Multiple epiphyseal dysplasia (MED) refers to an autosomal dominant clinical phenotype characterized by mild to moderate short stature associated with painful joints and precocious osteoarthritis. Historically, MED has been divided into the severe (or Fairbank) form and the mild (or Ribbing) form, although the phenotypes merge to form a gradient of severity. MED is a genetically heterogeneous condition.

MED mutations were first found in the gene encoding cartilage oligomeric matrix protein, COMP. This locus, which also harbors mutations responsible for pseudoachondroplasia, was designated *EDM1*. It was clear soon after the *EDM1* locus was identified that, in some families, MED does not map to the *COMP-EDM1* locus.

A second locus, designated *EDM2*, was identified in 1996 through positional cloning. It encodes the alpha 2 chain of type IX collagen, an extracellular matrix protein of cartilage and skeletal growth plate. This led to the view that type IX collagen and COMP interact functionally in growing bones and that disturbances of this interaction occur in pseudoachondroplasia and MED.

The existence of a third *EDM* locus was anticipated from linkage studies that excluded *EDM1* and *EDM2* in some families with MED phenotypes. The genes encoding the other 2 chains of type IX collagen, *COL9A1* and *COL9A3*, were the strongest candidates. *COL9A3* has now been identified as *EDM3*. Paassilta et al first established linkage of a relatively mild form of MED to a genetic marker in *COL9A3*. They next demonstrated a mutation predicted to disrupt splicing of *COL9A3* mRNA transcripts, leading to deletion of 12 amino acids near the amino-terminal end of the collagen chain. The mutation resembles the *COL9A2* mutation found in other cases of MED. Not surprisingly, the manifestations are similar in the families with type IX collagen mutations.

Paassilta P, et al. *Am J Hum Genet* 1999;64:1036-1044.

Editor's comment: *It is now evident that genes encoding cartilage matrix proteins are a very rich source of mutations that cause human chondrodysplasias. This reflects the importance of these proteins to endochondral bone growth. Since these proteins interact with each other to form a functional extracellular matrix, it makes sense that disturbances of different elements of this matrix lead to relatively similar clinical*

phenotypes. However, the mechanisms by which such disturbances interfere with bone growth remain poorly understood. Potential mechanisms include: (1) disturbances of the mechanical properties of cartilage, which must serve as a template for bone growth; (2) disturbances in the diffusion, sequestration, and/or presentation of growth factors; and (3) disturbances of direct interactions of the matrix with cartilage cells. As emphasis evolves in the post genome era from finding gene loci and detecting mutations to elucidating how mutations act, the mechanisms relevant to cartilage matrix protein mutations should be unveiled.

William A. Horton, MD

2nd Editor's comment: *MED must be thought of clinically in the presence of unexplained short stature (normal or abnormal proportions) and/or joint pains (particularly of the knees). Osteoarthritis results and frequently necessitates hip and knee replacement in adult life. In the current 4-generation family described by Paassilta et al, none of the 8 affected adults were outside the normal range for height. All had knee pain, often dating to childhood, and some had hip pain. A few had involvement of other joints. Clinical investigation should include radiologic examination, particularly of the knees and hips. X-ray studies of adults may or may not show abnormalities after epiphyseal fusion has occurred. Family history and investigation of short children and/or children with knee pain in the family may prove the diagnosis in the adult with suspected MED (by familial association).*

Robert M. Blizzard, MD

10 Years of Genomics, Chromosome 21, and Down Syndrome

Despite being the smallest of human chromosomes, chromosome 21 occupies a prominent place in human genetics. The long arm of this chromosome is approximately 37 mb in length and constitutes about 1% of the human genome. Trisomy for chromosome 21 is the most common aneuploidy at birth in humans; it results in the most common form of mental retardation, occurring in 1/700 live births. To celebrate the 10th birthday of the journal *Genomics*, Stylianos Antonarakis has written a comprehensive review covering the last decade of progress involving chromosome 21 and Down syndrome. The review covers diverse topics, including a comparison of different types of chromosome 21 maps; genes that may be responsible for the clinical phenotype in Down syndrome; genes that contribute to the pathogenesis of other disorders, including mouse models of Down syndrome; and the mechanisms that cause trisomy 21. The review also provides a good reference list of achievements in this area and insight into future progress that can be expected.

Antonarakis SE. *Genomics* 1998;51:1-16.

Editor's comment: *This 16-page article is an excellent review, especially for nongeneticists and geneticists who do not work in this field. It not only provides considerable information about chromosome 21 but also serves as a good tutorial on gene mapping strategies. Especially interesting is a discussion of how the many different types of genetic maps of chromosome 21 are related and how they are constructed. This review article is highly recommended to all our readers.*

William A. Horton, MD

Familial Defects in X-Inactivation

The molecular mechanism by which X-inactivation occurs is beginning to be elucidated. The process of X-inactivation is under the control of the X-inactivation center (XIC), which initiates and proliferates inactivation along the X chromosome. The active X chromosome *Xist* gene encodes and produces RNAs that coat the opposite X chromosome and seems to keep it inactive. Lee et al have shown there also is a *Tsix* element, which apparently lies within the XIC region and is expressed on the active X chromosome. High transcription levels of *Tsix* and *Xist* appear to be mutually exclusive. Interestingly, the transcript seems to overlap the *Xist* genes. How *Xist* and *Tsix* interrelate is not yet clear.

Naumova et al studied X-inactivation in normal women in families that are not known to have any genetic disease. They found quantitative differences among families with strong sister-to-sister correlations as to the degree of skewing from the expected 50% inactivation of each X chromosome. Interestingly, there is a lack of correlation between mothers and daughters. Lymphocytes were used for these studies, and it is certainly possible that other tissues might yield other results. The sister-to-sister correlation is consistent not only with a hereditary aspect of X-inactivation but also with the possibility that their phenotype is controlled by cis-acting gene. Also intriguing is the possibility that familial X-inactivation skewing involves differences in *Xist* and *Tsix* expression.

Heard E, et al. *Nature Genet* 1999;21:343-344.
Lee JT, et al. *Nature Genet* 1999;21:400-404.
Naumova AK, et al. *Eur J Hum Genet* 1998;1018:552-562.

Editor's comment: *X-inactivation is beginning to be unraveled. It is a wonderful model for gene control, identifying the mechanisms that may apply to both genomic imprinting and time-specific expression in tissues. The interesting correlation between sibs, but not mothers and daughters, in skewed X-inactivation families suggests that there is "cross talk" between the 2 X chromosomes. We all have been taught to expect 50-50 inactivation of the X chromosomes, but that appears to have been a generalization rather than a reality.*

Judith G. Hall, MD

A Novel Skeletal Dysplasia With Developmental Delay and Acanthosis Nigricans Is Caused By a LYS650MET Mutation in the Fibroblast Growth Factor Receptor 3 Gene

Mutations that cause the achondroplasia group of human chondrodysplasias map to a small number of codons in the fibroblast growth factor receptor 3 (*FGFR3*) gene. For example, almost everyone with typical achondroplasia has a mutation of codon 380, and all infants with the type II variant of thanatophoric dysplasia (TDII) have mutations at codon 650. This genetic homogeneity contrasts with the dispersion of mutations through host genes in many disorders that involve extracellular matrix proteins. There is now a new twist regarding *FGFR3* mutations.

Groups from California and Maryland have identified a novel clinical phenotype associated with a mutation of *FGFR3* codon 650 that is distinct from TDII. In TDII, the mutation changes the normal lysine at position 650 to a glutamic acid. A methionine residue is substituted for lysine 650 in the new disorder. This single amino acid difference produces substantial differences in manifestations.

Four unrelated patients were reported by Tavormina and colleagues. They all exhibited growth deficiency comparable to the type I variant of TD. However, they survived past infancy without prolonged life-support measures. The patients developed extensive areas of acanthosis nigricans beginning in early childhood, and they all suffered from severe neurologic impairment. The authors refer to the clinical phenotype as SADDAN (Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans). Lysine 650 resides in the activation loop of the tyrosine kinase domain of *FGFR3*, where it helps to regulate kinase activity in response to fibroblast growth factor ligand binding to the receptor. The kinase phosphorylates intracellular substrates, thereby initiating signals that influence bone growth. The TDII mutation has been shown to activate kinase activity in absence of ligand binding. A similar constitutive activation of kinase activity was demonstrated for the SADDAN mutation. In fact, the level of activation was higher for the SADDAN mutation than for TDII and achondroplasia mutations. The authors suggest that the SADDAN mutation may do more than activate the receptor in the absence of ligand. For example, it may affect downregulation of the activated receptor. They also suggest that the different amino acid substitution in SADDAN versus TDII may alter the specificity for substrate-signaling molecules that transmit *FGFR3* signals inside cells.

Tavormina PL, et al. *Am J Hum Genet* 1999;64:722-731.

Editor's comment: *The* FGFR3 *story continues to unfold. This report highlights the importance of the kinase region of the receptor, lysine 650 in particular, in understanding the pathogenesis of the achondroplasia group of disorders. It also underscores the importance of delineating differences in clinical phenotypes so that the functional consequences of mutations can be defined.*

The report raises some interesting questions. For example, is acanthosis nigricans a consequence of the SADDAN and not the TDII mutation? Or would TDII infants develop the skin lesions if they survived longer? Why is codon 650 so mutable? Will other mutations be found in FGFR3*, or have most or nearly all the mutations already been found, as is commonly believed?*

William A. Horton, MD

A Comparison of Target Height Estimated and Final Height Attained Between Swedish and Hong Kong Children

The investigators compared the target height (TH) equations of Luo et al, the final parental height method, derived for a Swedish population (see *GGH* 1999;15:13-14), and those of Tanner (derived from an English population) in Chinese subjects living in Hong Kong in whom adult stature was 10 to 12 cm less than that of the Swedish subjects. They found that on average the Tanner equations (corrected midparental height) underestimated adult stature by 4.5 cm, whereas the Luo equations gave values close to achieved mean adult heights in both males and females. However, there were wide ranges (±10 cm) of calculated TH for both sets of equations. The discrepancy between the 2 sets of TH prediction equations was exaggerated in subjects with low midparental heights. The authors conclude that the Luo equations are superior to the Tanner equations for estimation of TH.

Luo ZC, et al. *Acta Paediatr* 1999;88:248-252.

Editor's comment: *This article is brought to your attention as only a limited number of pediatricians know about the Luo equations (final parental height) method for estimation of TH, which may more accurately evaluate the effect of growth-promoting agents on the growth of pediatric patients. These equations have now*

been validated in a population in which adult height is far less and there is a secular trend for increased adult stature compared with that of the (stable) Swedish population. If the validity of the Luo equations is further confirmed, they will be more widely utilized and could replace the corrected midparental height of Tanner. Those of you who are particularly interested and/or concerned about the auxologic tools we use in clinical practice and in research will appreciate this article.

Allen W. Root, MD

Luo ZC, et al. *Pediatr Res* 1998;44:563-571.

Effects of Thyroxine as Compared With Thyroxine (T_4) Plus Triiodothyronine (T_3) in Patients With Hypothyroidism

The authors studied 33 patients receiving either replacement T_4 therapy for chronic lymphocytic thyroiditis (CLT) or suppressive therapy after near-total thyroidectomy because of thyroid cancer. Sixteen had CLT and 17 had thyroid cancer. Mean age was 46±13 years and mean T_4 dose was 175 ± 53 μg/d at baseline. After randomization, patients were assigned to receive T_4 alone for 5 weeks followed by $T_4 + T_3$ for 5 weeks or vice versa. On the last day of each 5-week period, thyrotropin, thyroid hormones, cholesterol, triglycerides, and sex hormone-binding protein (SHBP) were measured. Physiologic measurements, including pulse, blood pressure, electrocardiogram, sensory threshold, and Achilles tendon reflex, were recorded. Psychological assessment included cognitive function and psychological state.

Significant higher serum T_4 and free T_4 levels were found after T_4 treatment, compared with the combined treatment group. Significantly lower SHBP levels and heart rates also were observed during T_4 treatment. Conversely, after combined treatment, patients showed higher serum total SHBP levels and heart rates. However, those values remained within normal limits in both groups. Serum thyroid-stimulating hormone (TSH), cholesterol, triglycerides, blood pressure, sensory threshold, and Achilles tendon reflex relaxation half-time were similar with both treatment regimens. Significantly higher scores on the digit symbol test indicated better incidental learning, and the higher scores on the digit span test indicated improved mental flexibility and attention. After receiving $T_4 + T_3$, patients tended to be less depressed and experienced less fatigue-inertia, depression-dejection, and anger-hostility. At the end of the study, 20 patients preferred $T_4 + T_3$ treatment, 2 preferred T_4 alone, and 11 had no preference.

The authors concluded that patients with hypothyroidism may benefit from partial substitution of T_3, improving their mood and neuropsychological function.

Bunevicius R et al. *N Engl J Med* 1999;340:424-429.

Editor's comment: *Triiodothyronine treatment has been proven to be effective in several conditions, including myxedema coma and selective pituitary thyroid hormone resistance. In addition, Escobar-Morreale et al demonstrated that tissue euthyroidism and normal serum concentrations of T_3, T_4, and TSH were achieved in rats only with the administration of a combination of thyroid hormones (*Endocrinology *1996;137:490-502). In the present study, Bunevicius et al add data to support the potential significance of adding T_3 to the conventional T_4 therapeutic regimen in hypothyroidism. The authors demonstrated not only increases in serum T_3 levels but also improvements in mood and neuropsychological function without total suppression of TSH concentrations. However, long-term studies are necessary to establish the effectiveness of combined treatment with T_4 and T_3, in particular the long-term effects on bone mineralization and cardiovascular function.*

Fima Lifshitz, MD

Gene Mutations With Characteristic Deletions in Cord Blood T Lymphocytes Associated With Passive Maternal Exposure to Tobacco Smoke

The risks for cancer, heart disease, and other chronic illness are well known for adults who use tobacco, as are the risks for growth deficiency for fetuses exposed transplacentally to tobacco smoke. Now there is evidence that prenatal exposure to tobacco increases the risk for childhood malignancy. Finette et al used *HPRT* as a reporter gene to study the genetic consequences of tobacco exposure in utero. They analyzed *HPRT* mutations in cord blood T cells from newborn infants of mothers who had been exposed passively to tobacco smoke and of mothers with no known exposure. They searched especially for differences in types of mutations. The results showed the smoke-exposed infants harbored a higher frequency of a genomic deletion commonly associated with early childhood leukemias and lymphomas. The deletions are referred to as "illegitimate" mutational events because they are mediated by V(J)D recombinase activity, which normally mediates genomic rearrangements responsible for T-cell receptor and immunoglobulin diversity. The authors emphasized that the frequency of mutations was not statistically different between the 2 patient groups; rather, it was the type of mutations that differed. They noted that tobacco-derived nitrosamine derivatives from O6-methylguanine adducts have been detected in fetal cord blood of leukocyte DNA of primates and raise the possibility that these adducts could be related mechanistically to the mutations.

Unfortunately, too few T-cell clones were isolated from infants whose mothers had smoked to be included in the analysis. The authors, as well as the authors of an accompanying editorial (Sozzi G, et al. *Nat Med* 1998;4:1119-1120) cautioned that the results need to be confirmed by other studies.

Finette BA, et al. *Nat Med* 1998;4:1144-1151.

Editor's comment: *This is an intriguing article because of its clinical implications. The following is abstracted from the editorial by Sozzi et al appearing in the same issue:*

"Although epidemiologic studies have suggested that maternal and paternal passive smoke exposure increases cancer risk in children, the Finette study is the first demonstration of smoking-induced genetic damage in utero. It is noteworthy that a recent study by Hecht and colleagues (presented in August at the American Chemical Society meeting) found that urine from 19 of 31 neonates born to mothers that smoked during pregnancy contained metabolites of NNK (4-methylnitrosamino-1-(-3pyridyl)-1-butanone), a carcinogen found only in tobacco smoke. Metabolites were not found in urine samples from any infants born to non-smoking mothers.

Given the small sample size of the Finette study, additional investigations of the transplacental effects of passive smoke in newborns are required. These studies should include analysis of transplacental exposure of preterm infants and newborns to 'active' as well as passive cigarette smoke. (In adults a similar spectrum of p53 mutations in lung tumors from passive and active smokers has been found.) In addition, measurement of the 'rate' of tobacco consumption in actively smoking mothers as well as a more precise quantitation of passive smoke exposure in non-smoking mothers should be obtained. V(D)J-recombinase-mediated HPRT *deletions also occur spontaneously, thus the comparison of these changes in exposed and in unexposed groups is critical.*

This study provides incontrovertible genetic evidence of the devastating effects of tobacco smoke particularly among the young, who suffer a greater risk from environmental toxicants, such as tobacco smoke, not only because of their smaller size but also because of their physiological immaturity. The time has come to proclaim an end to the exposure of preterm infants, newborns, and children of all ages to tobacco smoke."

My opinion is possibly a little more cautious than that of Sozzi et al. I agree the results must be confirmed. The causative nature of the deletions needs to be established before drawing firm conclusions. If the risk turns out to be true, the article provides an additional reason not to expose fetuses to tobacco smoke.

William A. Horton, MD

Monthly Measurements of IGF-1 and IGFBP-3 In Healthy Prepubertal Children: Characterization and Relationship With Growth: The 1-Year Growth Study

Gelander et al studied 65 prepubertal healthy children (38 boys and 27 girls) between the ages of 8 and 11 years (mean, 9.1 ± 0.85 years) with monthly determinations of insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3). In addition, measurements of height, weight, and lower leg length (using a knemometer) were recorded monthly by the same person between 0800 and 1000 hours. All biochemical analyses for each child were performed in the same assay. Additional data, including recent illness, food intake, and the daily mean temperature and number of hours of sunshine, also were recorded. Since concentrations of IGF-1 and IGFBP-3 are age dependent, the values were converted to SDS using prepubertal reference values.

Mean levels of IGF-1 in the children were significantly higher for the girls than for the boys ($P < 0.05$). By multiple stepwise regression analysis, height SDS, gender, and height velocity were significant parameters that explained 45% of the variance in IGF-1 SDS. The mean coefficient of variation for IGF-1 adjusted for age for each child was 13.9%, with a mean difference between samples taken at 3 monthly intervals from -0.4 to +0.3. These changes were correlated with changes in body mass index, but also were influenced negatively by illness and positively by outdoor temperature. Maximum changes over 3 months were related only to changes in temperature. The mean serum concentration of IGFBP-3 was comparable in boys and girls and correlated with the height SDS, weight SDS, height velocity, and weight gain. By using multiple regression analysis, 33% of the level of IGFBP-3 could be explained by gender, height SDS, and weight gain. The mean coefficient of variation for IGFBP-3 was 9.7%, and changes in IGFBP-3 were not related to recent illnesses and changes in body mass index. However, the changes in IGFBP-3 over 1 and 3 months correlated with season, evaluated as either changes in the outdoor temperature or hours of sunshine.

The authors noted that their data demonstrate considerable monthly variation in both IGF-1 and IGFBP-3 of such a magnitude that it exceeds the analytical precision of the measurements. This information needs to be carefully considered when evaluating a single IGF-1 or IGFBP-3 concentration in a child who is not growing or whose growth is being evaluated. If repeated IGF-1 concentrations are to be used to evaluate treatment, the changes must exceed -0.4 to +0.4 SDS, whereas the changes for IGFBP-3 must exceed -0.6 to +0.3 to reflect a significant treatment effect. The data also demonstrate the importance of following more than 1 auxologic or biochemical variable. The seasonal variation in growth also has been demonstrated with these changes in IGF-1 and IGFBP-3.

Gelander L, et al. *Pediatr Res* 1999;45:377-383.

Editor's comment: *This is an interesting, well-conducted study. The type of carefully collected information that Gelander and colleagues have provided can be of significant use in interpreting biochemical growth variables in short children, even those not receiving exogenous growth hormone. Knowing the coefficient of variation around the child's IGF-1 or IGFBP-3 level enhances the physician's ability to determine whether changes in these parameters are of biologic significance. Finally, it is of interest to have verification of the frequently observed finding that children grow up better when the weather is warmer.*

William L. Clarke, MD

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Instructions: The Post-Program Self-Assessment/Course Evaluation Answer Sheet can be found on the center page of the issue. Please follow the instructions listed there to receive CME Category 1 credit.

1. Gender identity determines
   a) gender role.
   b) psychosexual preference.
   c) the pregnancy rate in females with SVCAH.
   d) self-image.

2. There is almost full agreement among investigators regarding which one(s) of the following:
   a) that estrogen in utero influences determination of the gender role in females.
   b) that testosterone influences in utero the gender role.
   c) that testosterone in utero affects the incidence of learning disabilities.
   d) that Müllerian inhibiting factor affects gender identity.

3. Growth in CAH patients correlates directly with which one(s) of the following:
   a) basal metabolic rate.
   b) birth weight.
   c) midparental height.
   d) time of onset of menarche.
   e) none of the above.

4. Data suggest that CAH patients who undergo adrenalectomy as treatment will grow taller than those medically treated.
   a) true
   b) false

5. The pregnancy potential in CAH females can be monitored by using
   a) progesterone serum levels to estimate libido.
   b) 17-ketosteroids to determine libido.
   c) progesterone levels to modulate whether ovulation has occurred.

Answer Key: 1. d 2. b,c 3. d 4. b 5. c

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